DYNAMO

Diabetes studY in Nephropathy And other Microvascular cOmplications

Addressing the Challenge of Diabetic Kidney Disease in Singapore

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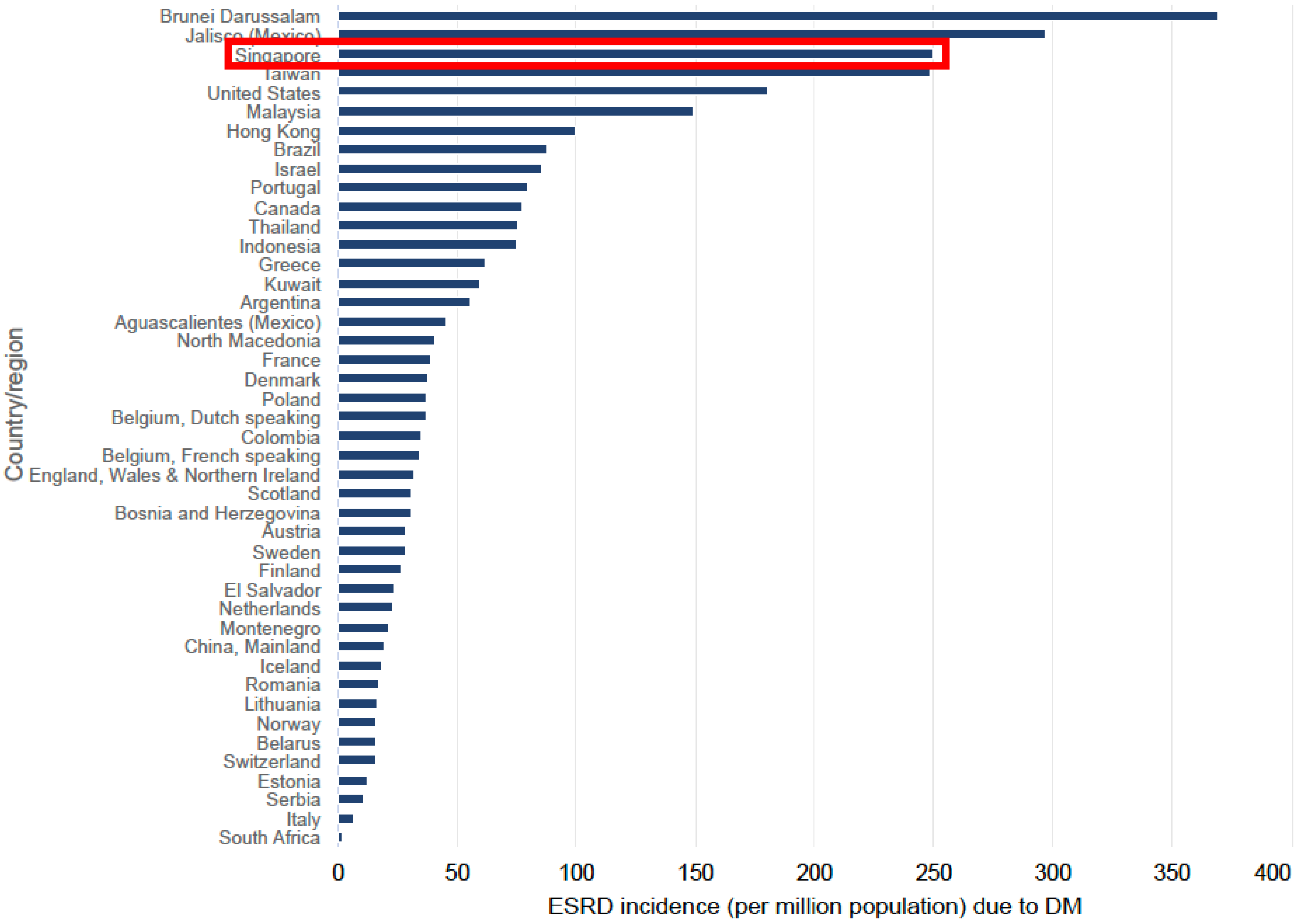
Duke University School of Medicine

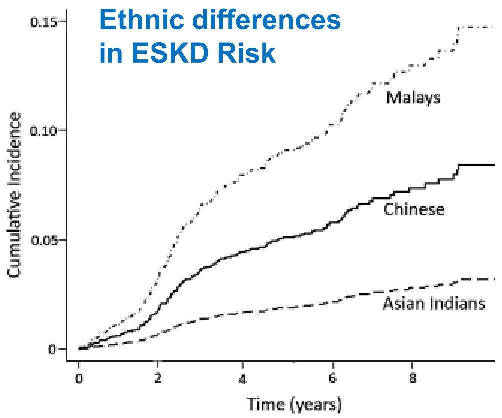
Diabetic Kidney Disease in Singapore

Incidence of diabetes as a cause of ESKD in 2021 (*USRDS 2023 Annual Data Report*)



Singapore #5 in the world in adjusted global prevalence of ESKD (*Am J Nephrol* 2021;52:98–107)

≈66% of new cases of ESKD in Singapore are due to diabetes (*Singapore Renal Registry Annual Report* 2021)



Liu JJ et al *Diabet Med* 33:332-339 (2016)

DYNAMO: Objectives

- **Address major unmet needs by identifying new mechanistic pathways in Diabetic Nephropathy**

- **Discovering and validating potential new targets for treatment**

- **Defining novel biomarkers and strategies allowing early stratification of risk for DN within the larger population of people with type 2 diabetes**

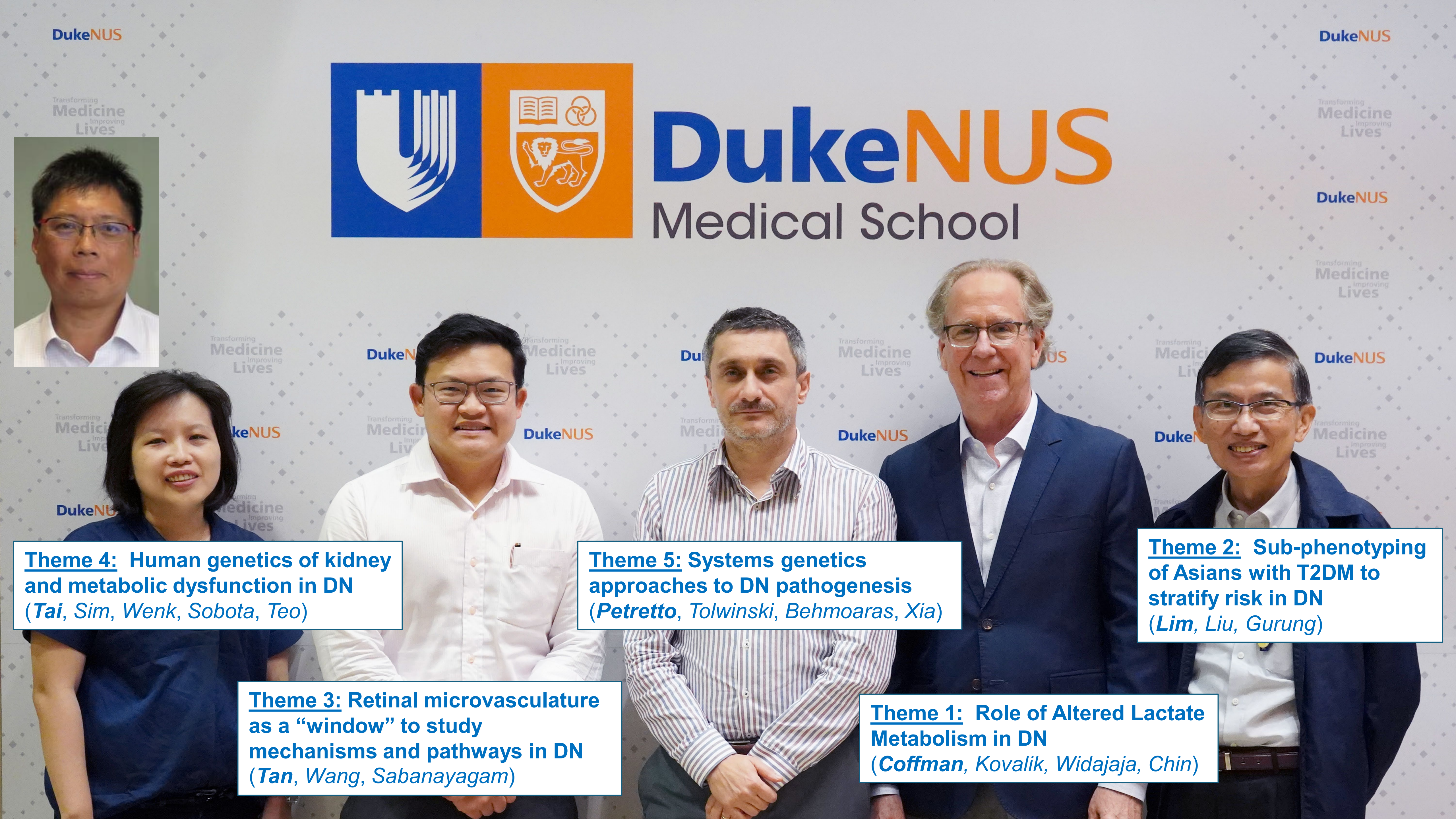
25 Institutions

6 countries

30,000+ Patients
in 6 clinical cohorts

70 Investigators

Table 1	SEED	KTPH Diabetic Nephropathy	SMART 2D	The Diabetes Cohort	NUH DKD Cohort	SIDRP	SGH DKD Cohort*
Subjects w/ blood and/or urine samples	1,564	6,840	2,067	14,068	200	*	62
Whole Genome Sequences	69	724	498	655	-	-	-
GWAS Array w/ imputation	2,214	4,875	2,264	5,845	-	-	-
Retinal Photographs	2,877	1,166	-	-	-	22,463	-
Metabolomics	2,785	1,032	2,030	4,998	-	-	-
Lipidomics		1,031	2,029	4,989			
Targeted Proteomics	-	-	300	-	-	-	-
Non-targeted Proteomics	-	-	300	-	-	-	-
Kidney Biopsy w/ Transcriptomics	-	-	-	-	40	-	62

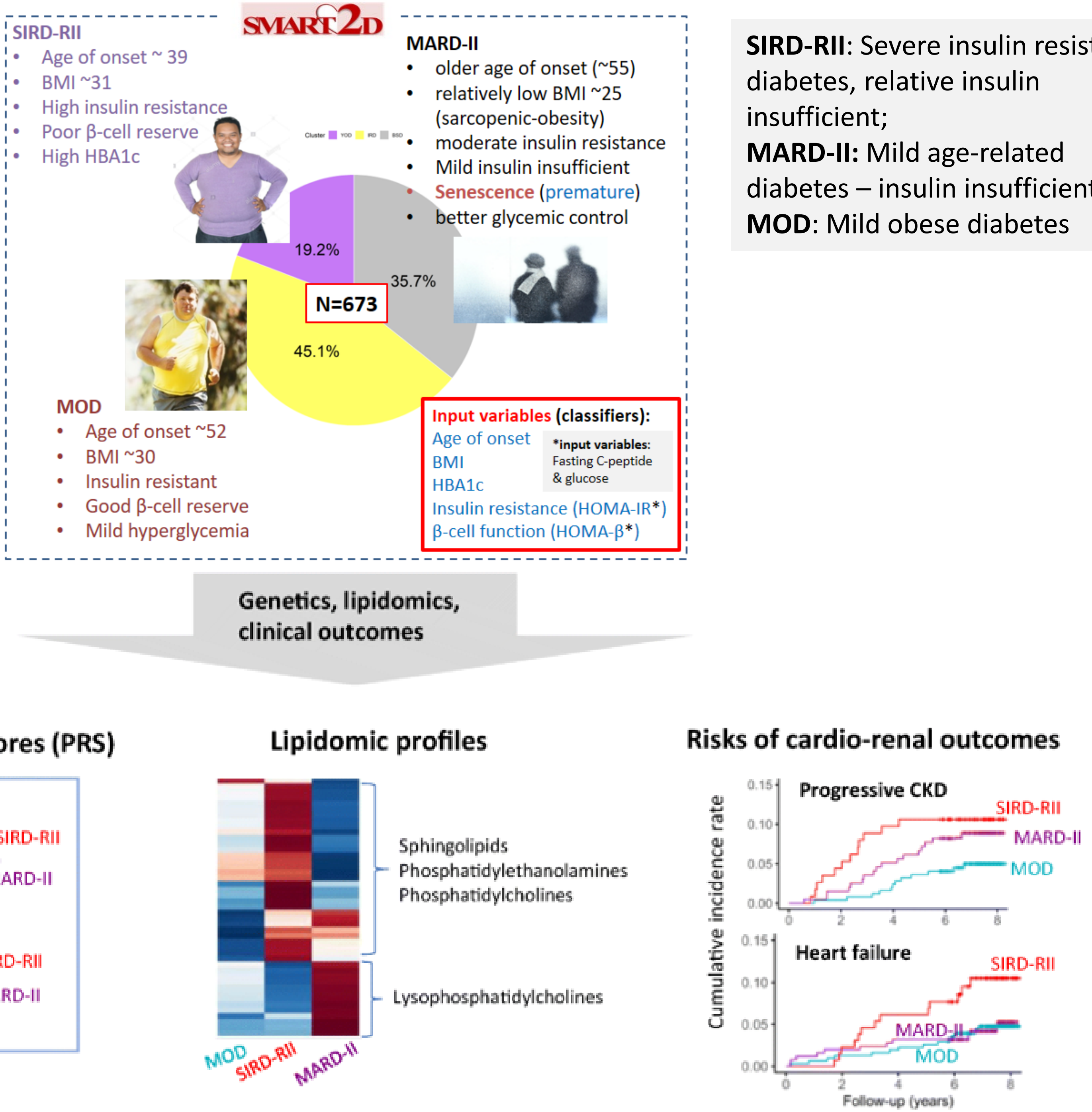

Duke NUS
Medical School
Theme 4: Human genetics of kidney and metabolic dysfunction in DN
(Tai, Sim, Wenk, Sobota, Teo)
Theme 3: Retinal microvasculature as a "window" to study mechanisms and pathways in DN
(Tan, Wang, Sabanayagam)
Theme 5: Systems genetics approaches to DN pathogenesis
(Petretto, Tolwinski, Behmoaras, Xia)
Theme 1: Role of Altered Lactate Metabolism in DN
(Coffman, Kovalik, Widajaja, Chin)
Theme 2: Sub-phenotyping of Asians with T2DM to stratify risk in DN
(Lim, Liu, Gurung)

Theme 2

Clinical variable-based cluster analysis identifies novel subgroups with a distinct genetic signature, lipidomic pattern and cardio-renal risks …ecent-onset type 2 diabetes

Diabetologia (2022) 65:2146–2156

Jiexun Wang, Jian-Jun Liu, Resham L. Gurung, Sylvia Liu, Janus Lee, Yiamunaa M, Keven Ang, Yi Ming Shao, Justin I-Shing Tang, Peter I. Benke, Federico Torta, Markus R. Wenk, Subramaniam Tavintharan, Wern Ee Tang, Chee Fang Sum, Su Chi Lim



SIRD-RII: Severe insulin resistant diabetes, relative insulin insufficient;
MARD-II: Mild age-related diabetes – insulin insufficient;
MOD: Mild obese diabetes

Theme 3

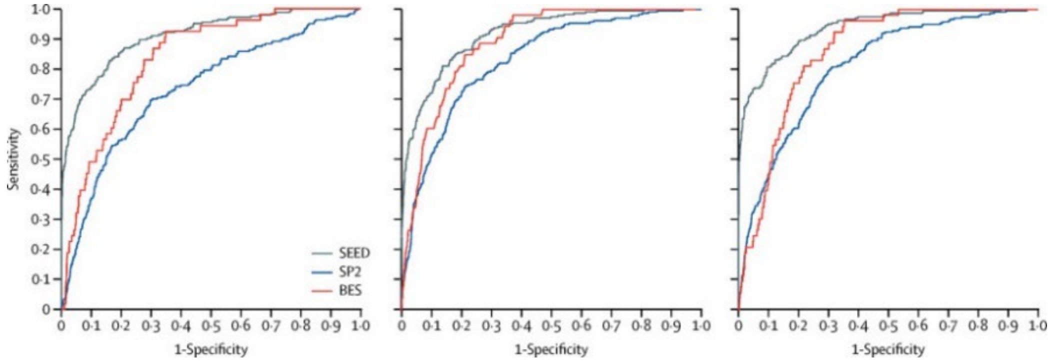
Predicting CKD with AI and Retinal Optical Coherence Tomography

A deep learning algorithm to detect chronic kidney disease from retinal photographs in community-based populations

Charumathi Sabanayagam, Dejiang Xu, Daniel S W Ting, Simon Nusinovici, Riswana Banu, Haslina Hamzah, Cynthia Lim, Yih-Chung Tham, Carol Y Cheung, E Shyong Tai, Ya Xing Wang, Jost B Jonas, Ching-Yu Cheng, Mong Li Lee, Wynne Hsu, Tien Y Wong

Summary
Background Screening for chronic kidney disease is a challenge in community and primary care settings, even in high-income countries. We developed an artificial intelligence deep learning algorithm (DLA) to detect chronic kidney disease from retinal images, which could add to existing chronic kidney disease screening strategies.

Lancet Digital Health 2020; 2: e295–302
Published Online May 12, 2020

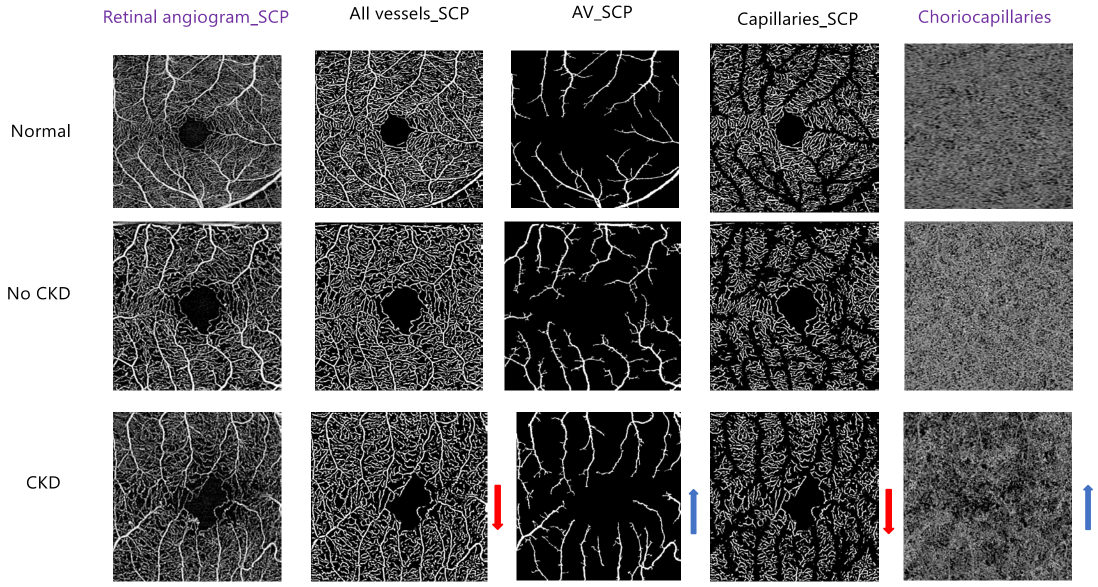


Clinical science

OPEN ACCESS

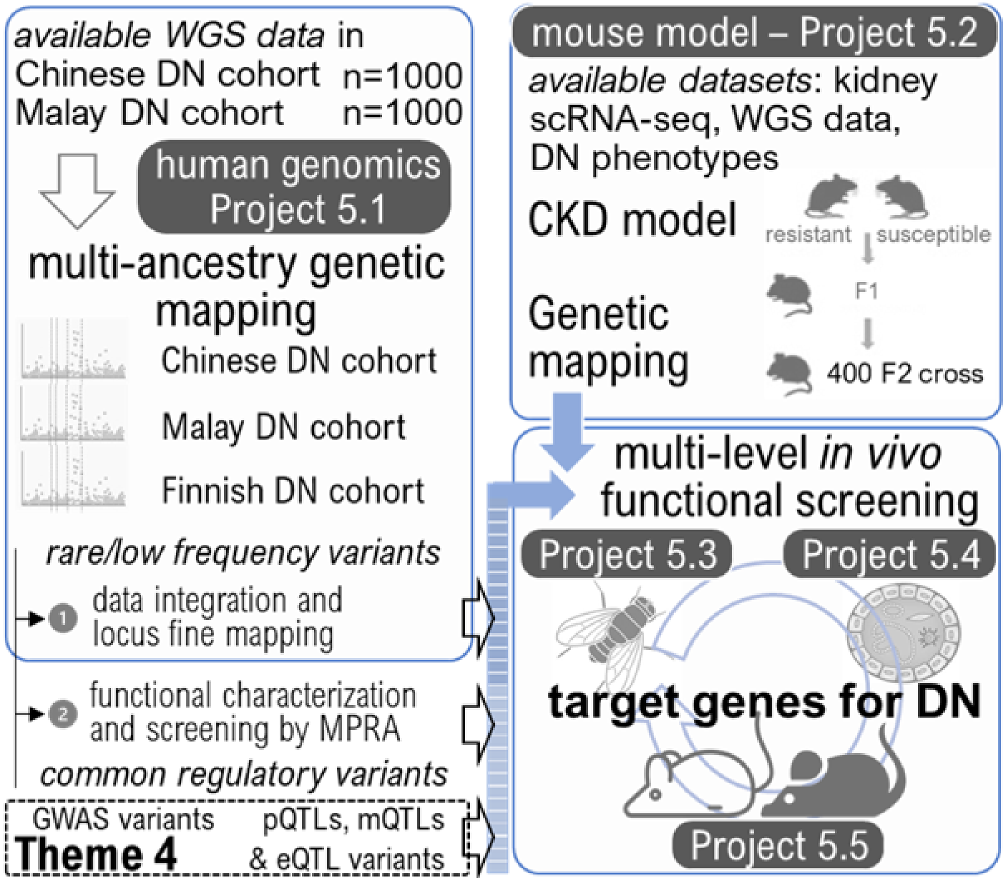
Combining retinal and choroidal microvascular metrics improves discriminative power for diabetic retinopathy

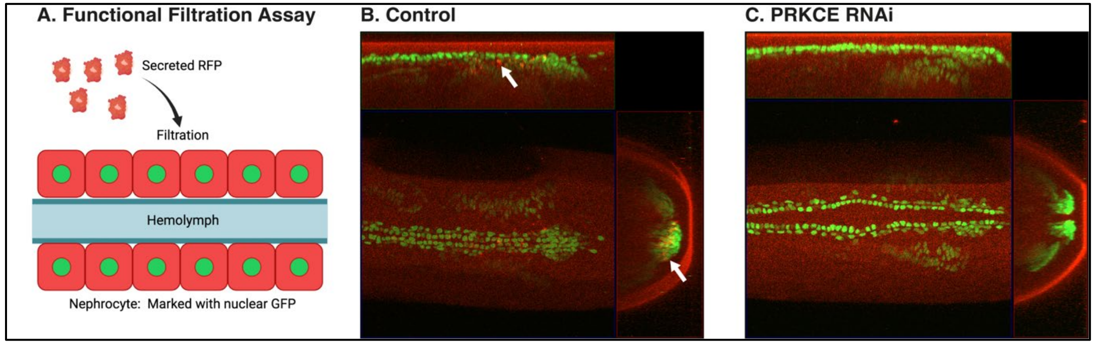
Bingyao Tan,[1,2,3] Nicole-Ann Lim,[1,4] Rose Tan,[1,5] Alfred Tau Liang Gan,[1] Jacqueline Chua,[1,2,5,6] Simon Nusinovici,[1,6] Chui Ming Gemmy Cheung,[1,5,6] Usha Chakravarthy,[7] Tien Yin Wong,[1,5,6] Leopold Schmetterer,[1,2,3,4,6,8] Gavin Tan[1,5,6]

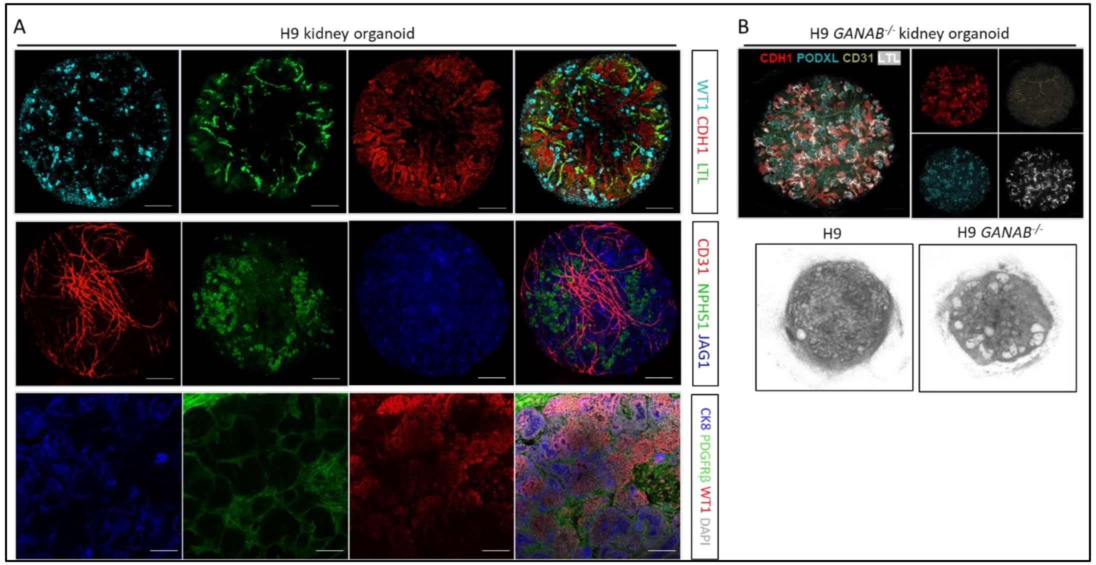


Themes 4 & 5

Genetic Mechanisms in DN Pathogenesis







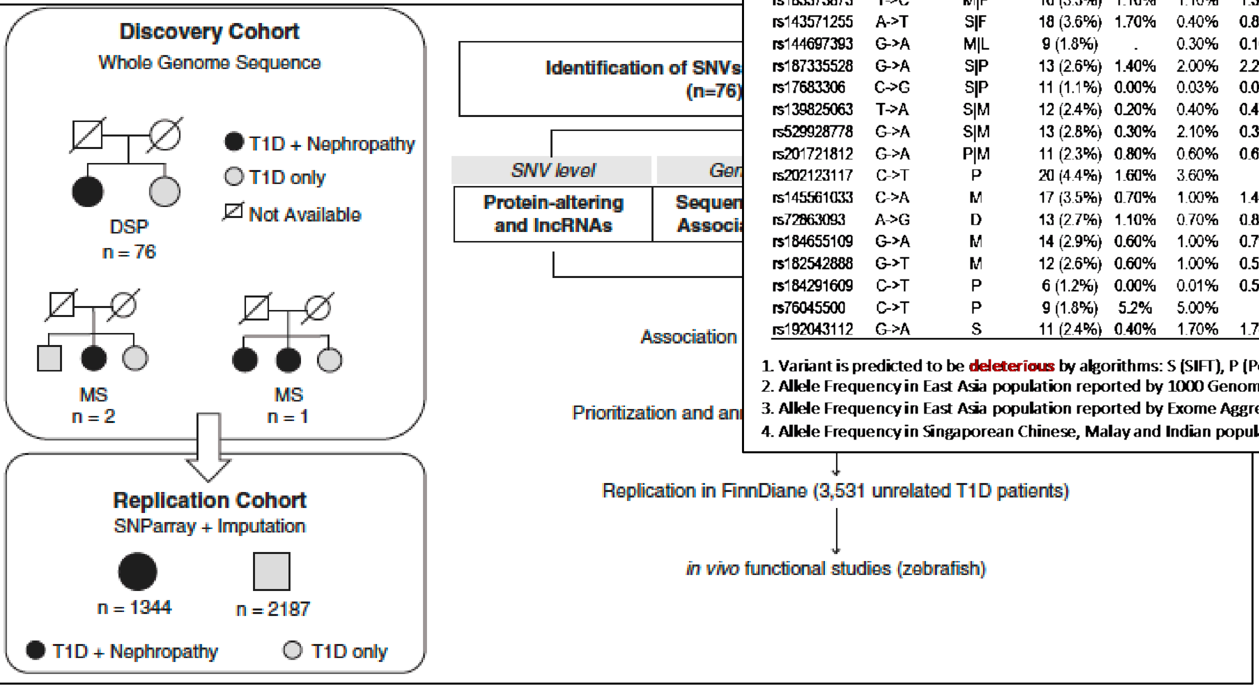
Theme 5

Systems genetics approaches to DN pathogenesis

BASIC RESEARCH www.jasn.org

Whole-Genome Sequencing of Finnish Type 1 Diabetic Siblings Discordant for Kidney Disease Reveals DNA Variants associated with Diabetic Nephropathy

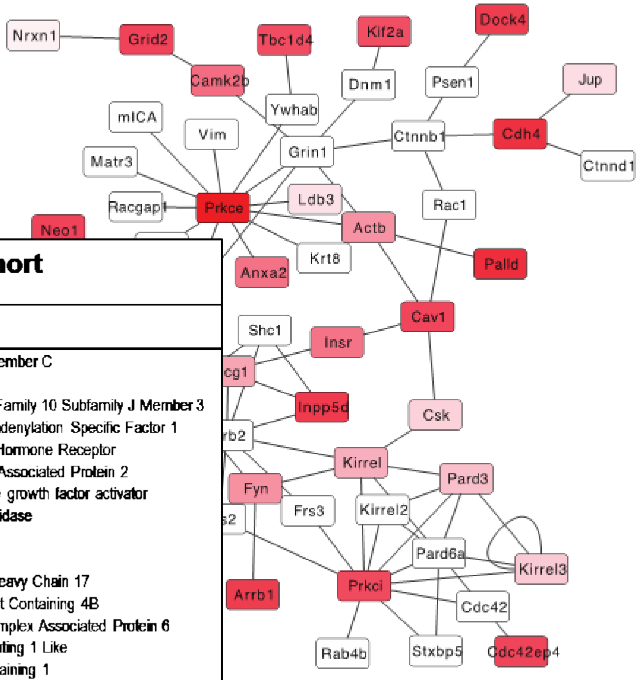
Jing Guo,[1,2] Owen J. L. Rackham,[2] Niina Sandholm,[3,4,5] Bing He,[1] Anne-May Österholm,[1,2] Erkka Valo,[3,4,5] Valma Harjutsalo,[3,4,5,6] Carol Forsblom,[3,4,5] Iiro Toppila,[3,4,5] Maija Parkkonen,[3,4,5] Qibin Li,[7] Wenjuan Zhu,[7] Nathan Harmston,[2,8] Sonia Chothani,[2] Miina K. Öhman,[2] Eudora Eng,[2] Yang Sun,[2] Enrico Petretto,[2,9] Per-Henrik Groop,[3,4,5,10] and Karl Tryggvason[1,2,11]

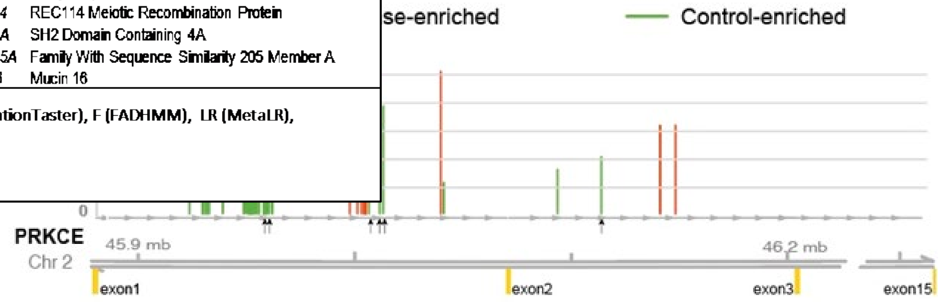


Pathogenic mutations carried only by DN cases in the Chinese cohort

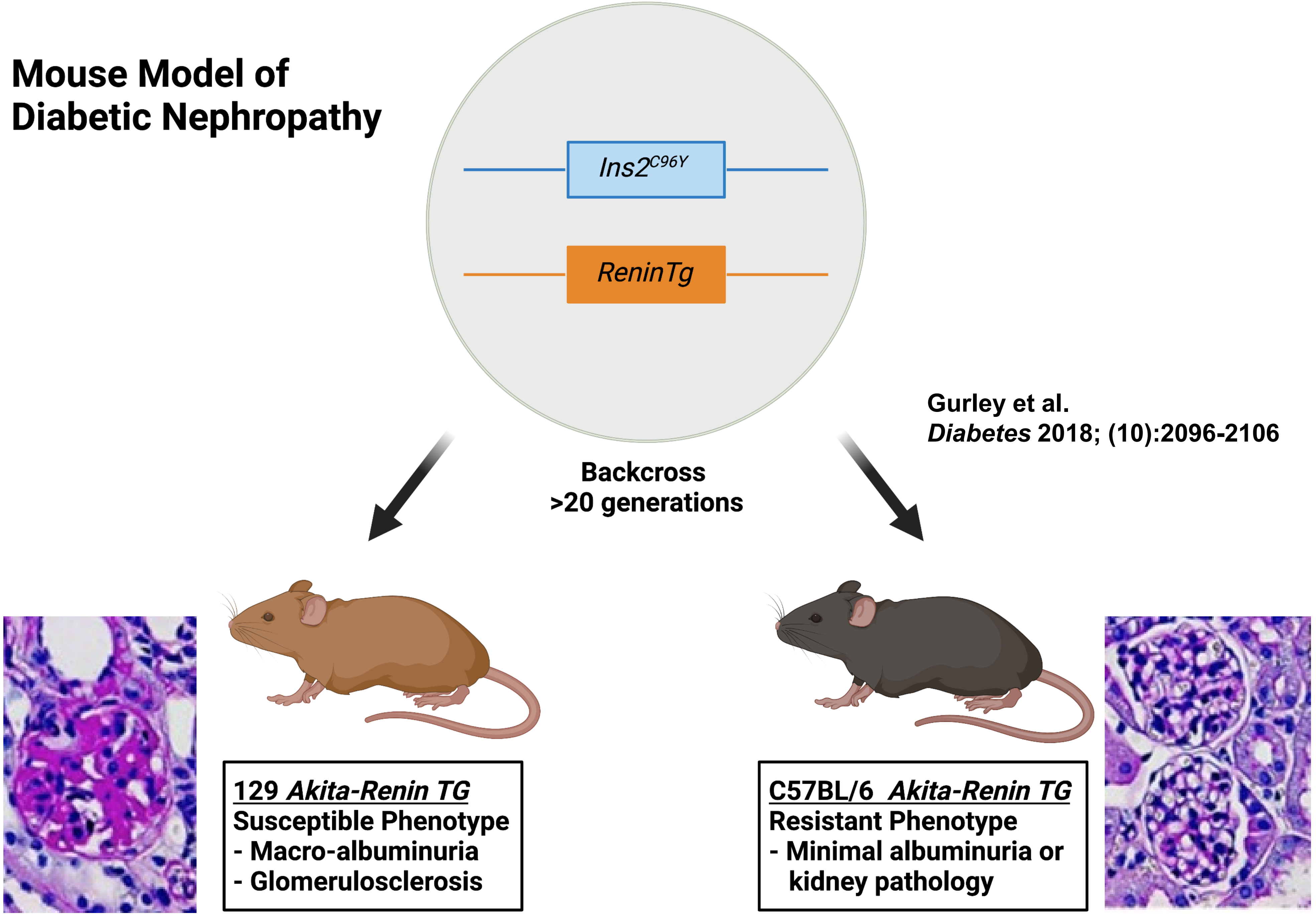
SNV ID		Variant Function Prediction[1]	DN cases N (%)	1000G[2]	ExAC[3]	Chinese	Malay	Indian	Gene	
rs567408718	C->T	S|P|M|L	11 (2.2%)	0.12%	0.05%	0.28%	0.22%	0.00%	*GOLGA6C*	Golgin A6 Family Member C
rs199959926	G->C	F|R|LR	9 (1.9%)	0.14%	0.04%	1.14%	1.32%	0.06%	*FLNB*	Filamin B
rs202163099	A->T	S|P|M	10 (2.2%)	.	0.40%	0.28%	0.22%	0.00%	*OR10J3*	Olfactory Receptor Family 10 Subfamily J Member 3
rs139223635	G->C	P|M|L	11 (2.2%)	0.20%	0.60%	0.63%	0.00%	0.00%	*CPSF1*	Cleavage And Polyadenylation Specific Factor 1
rs190096402	C->A	M|F|LR	10 (2.0%)	0.20%	0.10%	0.12%	0.00%	0.00%	*FSHR*	Follicle Stimulating Hormone Receptor
rs183373873	T->C	M|F	16 (3.3%)	1.10%	1.10%	1.34%	0.11%	0.00%	*CLASP2*	Cytoplasmic Linker Associated Protein 2
rs143571255	A->T	S|F	18 (3.6%)	1.70%	0.40%	0.83%	5.29%	0.12%	*HGFAC*	Activates hepatocyte growth factor activator
rs144697393	G->A	M|L	9 (1.8%)	.	0.30%	0.16%	0.22%	0.00%	*ENPEP*	Glutamyl Aminopeptidase
rs187335528	G->A	S|P	13 (2.6%)	1.40%	2.00%	2.29%	0.22%	0.12%	*EPPK1*	Epiplakin 1
rs17683306	C->G	S|P	11 (1.1%)	0.00%	0.03%	0.00%	0.00%	0.00%	*FSTL4*	Follistatin Like 4
rs139825063	T->A	S|M	12 (2.4%)	0.20%	0.40%	0.47%	0.00%	0.00%	*DNAH17*	Dynein Axonemal Heavy Chain 17
rs529928778	G->A	S|M	13 (2.8%)	0.30%	2.10%	0.36%	0.22%	0.00%	*LRRC4B*	Leucine Rich Repeat Containing 4B
rs201721812	G->A	P|M	11 (2.3%)	0.80%	0.60%	0.67%	1.32%	0.00%	*TUBGCP6*	Tubulin Gamma Complex Associated Protein 6
rs202123117	C->T	P	20 (4.4%)	1.60%	3.60%	.	.	.	*MST1L*	Macrophage Stimulating 1 Like
rs145561033	C->A	M	17 (3.5%)	0.70%	1.00%	1.46%	5.18%	0.37%	*RCSD1*	RCSD Domain Containing 1
rs72863093	A->G	D	13 (2.7%)	1.10%	0.70%	0.83%	1.76%	7.13%	*RASSF6*	Ras Association Domain Family Member 6
rs184655109	G->A	M	14 (2.9%)	0.60%	1.00%	0.79%	0.66%	0.00%	*NMT2*	N-Myristoyltransferase 2
rs182542888	G->T	M	12 (2.6%)	0.60%	1.00%	0.51%	0.00%	0.00%	*REC114*	REC114 Meiotic Recombination Protein
rs184291609	C->T	P	6 (1.2%)	0.00%	0.01%	0.56%	0.11%	0.00%	*SH2D4A*	SH2 Domain Containing 4A
rs76045500	C->T	P	9 (1.8%)	5.2%	5.00%	.	.	.	*FAM205A*	Family With Sequence Similarity 205 Member A
rs192043112	G->A	S	11 (2.4%)	0.40%	1.70%	1.74%	0.55%	0.00%	*MUC16*	Mucin 16

1. Variant is predicted to be **deleterious** by algorithms: S (SIFT), P (PolyPhen2), L (LRD,) M (MutationTaster), F (FADHMM), LR (MetaLR),
2. Allele Frequency in East Asia population reported by 1000 Genome Project Phase III
3. Allele Frequency in East Asia population reported by Exome Aggregation Consortium (ExAC)
4. Allele Frequency in Singaporean Chinese, Malay and Indian populations reported by



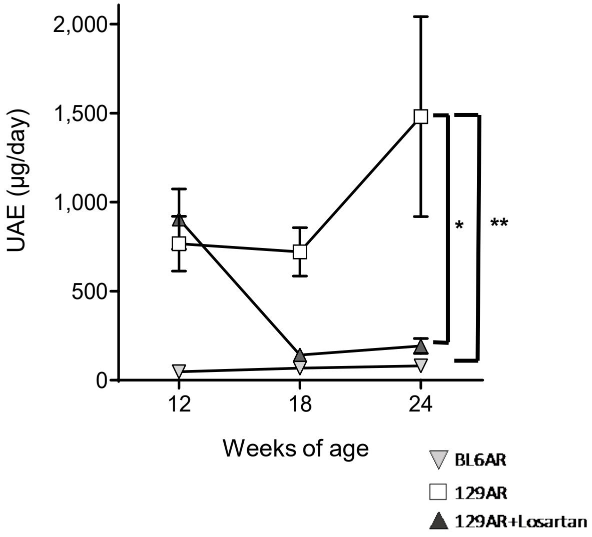


Theme 1: Role of Altered Lactate Metabolism in Diabetic Nephropathy


Mouse Model of
Diabetic Nephropathy
Ins2C96Y
ReninTg
Gurley et al.
Diabetes 2018; (10):2096-2106
Backcross
>20 generations
129 Akita-Renin TG
Susceptible Phenotype
- Macro-albuminuria
- Glomerulosclerosis
C57BL/6 Akita-Renin TG
Resistant Phenotype
- Minimal albuminuria or
kidney pathology

ARB Treatment Abolishes Albuminuria and Improves Kidney Pathology in a Mouse Model of Diabetic Nephropathy

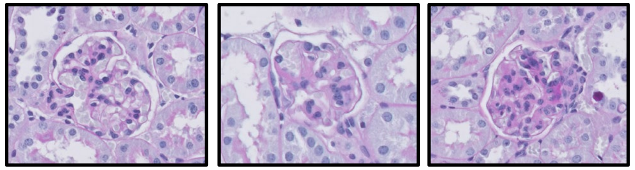
Albuminuria



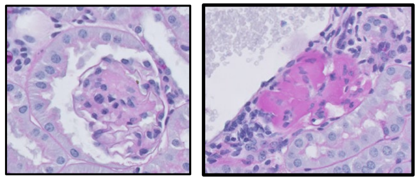
Kidney Pathology

Experimental Groups	Total Score	Mesangial Expansion	Nodular Sclerosis	Global Sclerosis
129 AR (Veh)	3.7±2.4	2.9±0.8	33%	50%
C57BL/6 AR	1.6±0.3 *	1.6±0.3*	0	0

Mesangial Expansion Scores



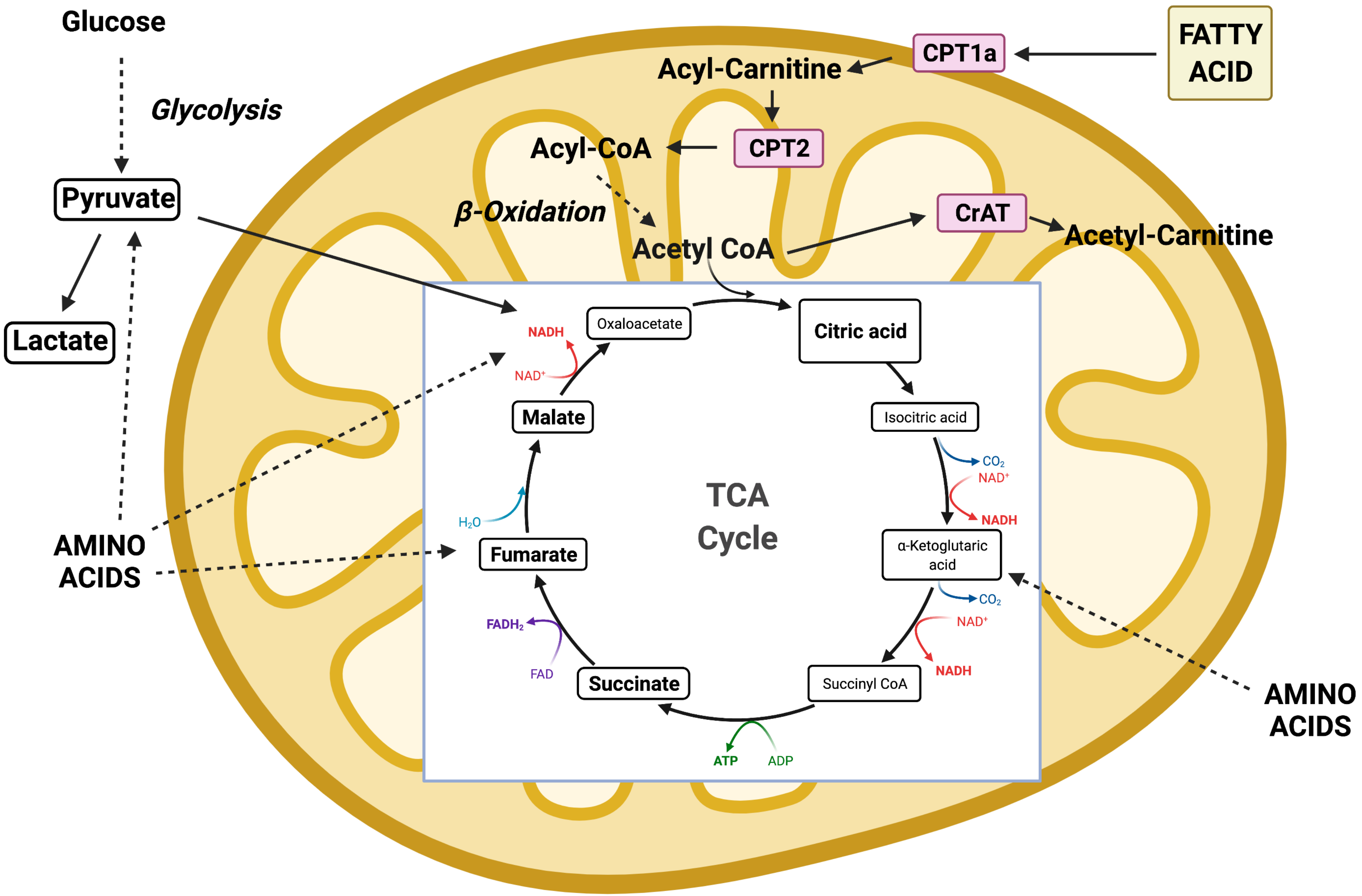
+1 **+2** **+3**



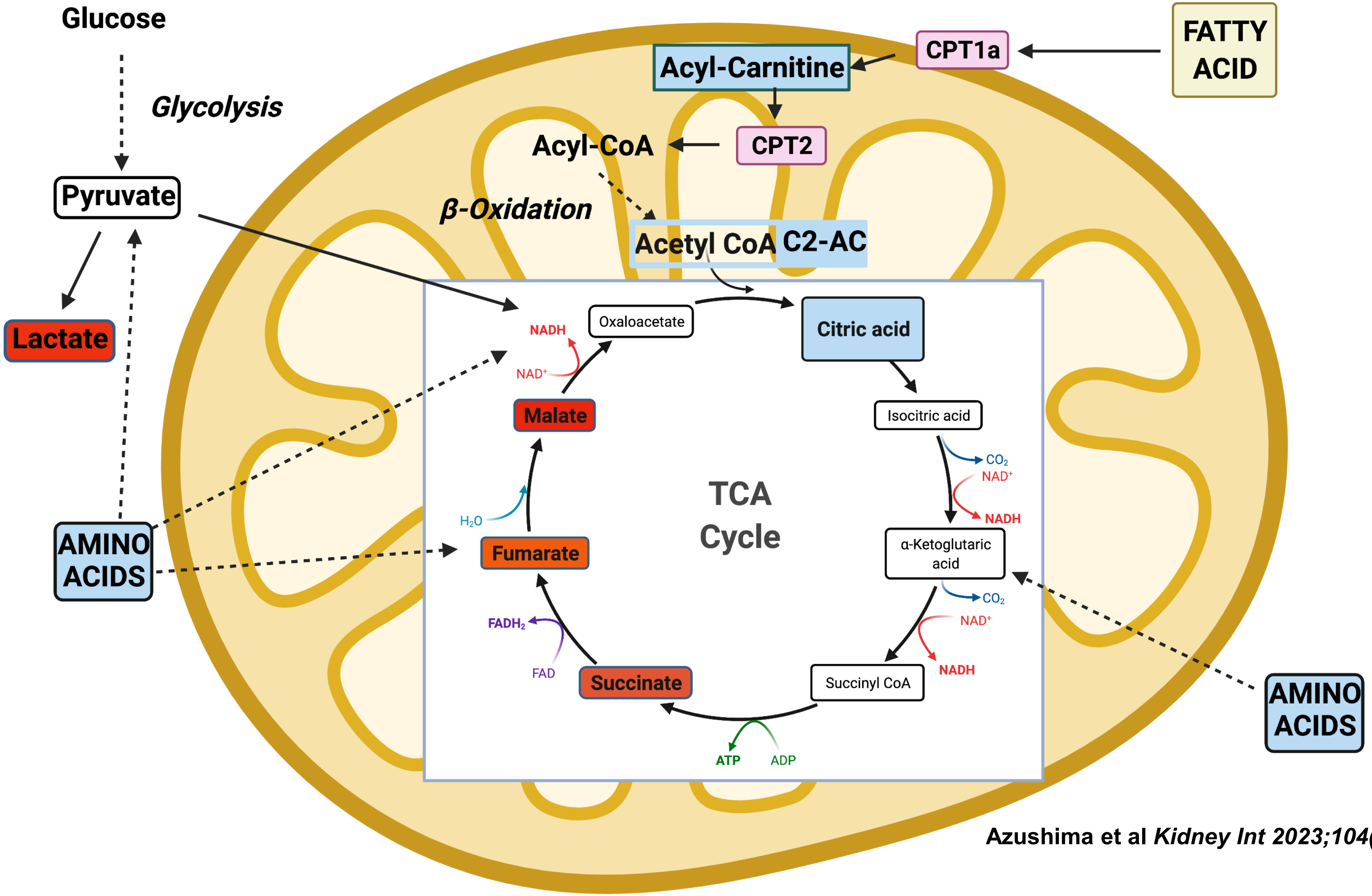
Nodular Sclerosis **Global Sclerosis**

Azushima et al *Kidney International* (2023) doi.org/10.1016

Kidney Metabolism in Diabetic Kidney Disease



Metabolic Alterations in Kidneys of 129AR Mice



Azushima et al *Kidney Int 2023;104(6):1135-1149*

Lactate and TCA Cycle Metabolites in DKD

Mouse Kidney

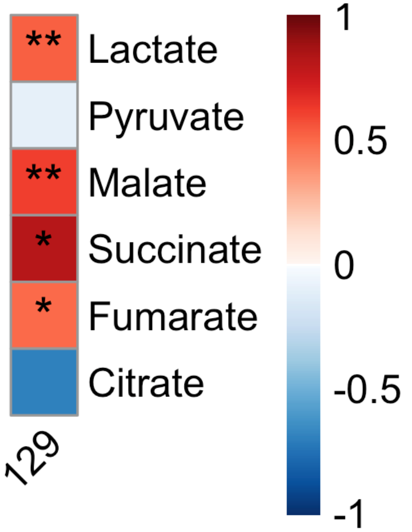


Table 2. Baseline Urine TCA Cycle Metabolite Levels (nM in 4 mM Creatinine) in Discovery and Validation Studies

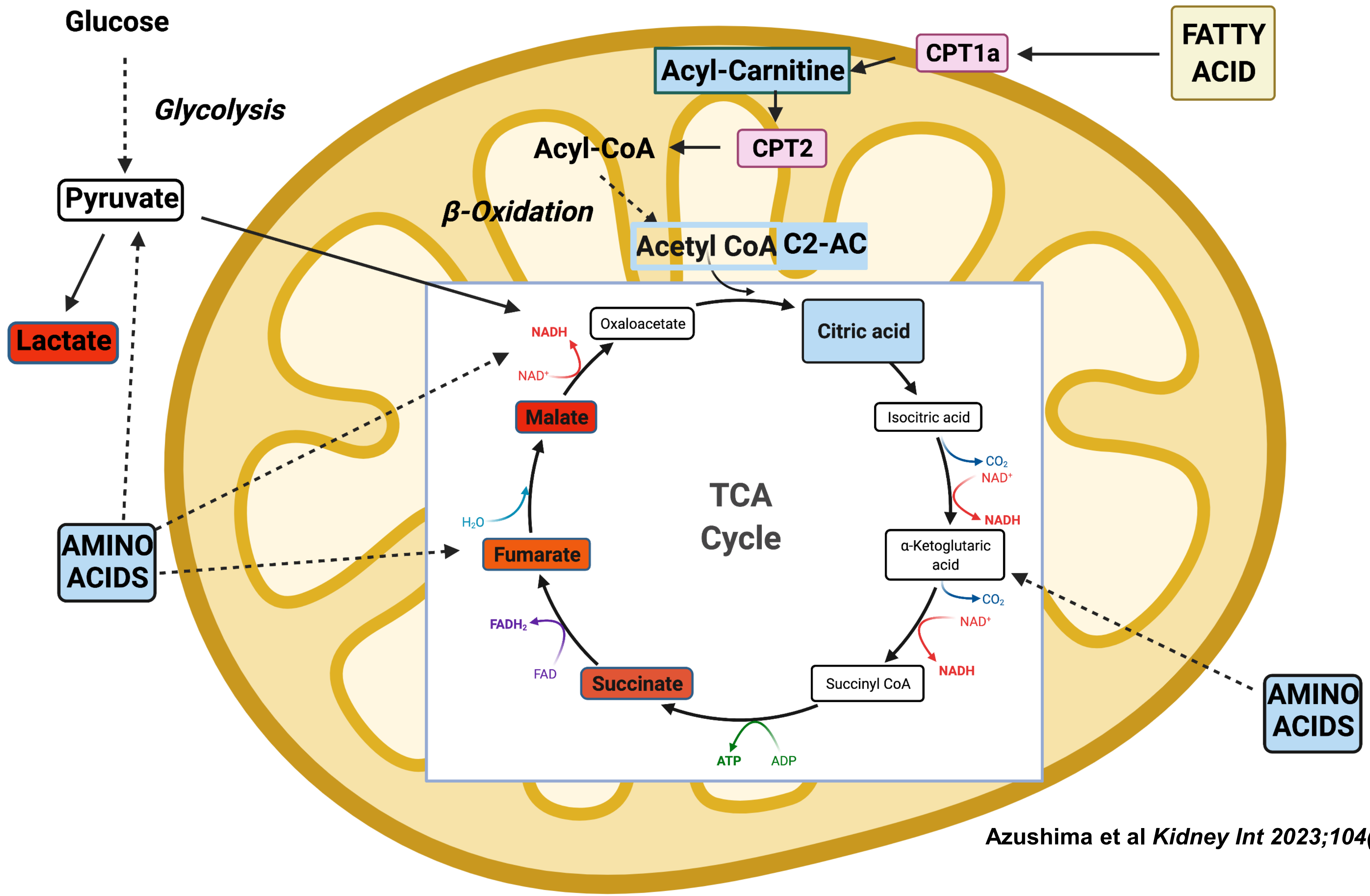
	Discovery Study			Validation Study		
	Nonprogressors (Controls, n = 271)	CKD Progressors (Cases, n = 116)	*P* Value[a]	Nonprogressors (Controls, n = 402)	CKD Progressors (Cases, n = 96)	*P* Value[a]
Lactate	**158 (96–295)**	**212 (141–498)**	**2.6×10^{-4}**	**215 (142–348)**	**239 (165–412)**	**0.02**
Pyruvate	140 (91–230)	161 (97–237)	0.12	117 (83–154)	126 (101–158)	0.01
Citrate	**1060 (602–1713)**	**754 (329–1491)**	**0.001**	**1266 (810–1685)**	**936 (505–1644)**	**3.1×10^{-5}**
α-Ketoglutaric acid	94 (52–172)	132 (64–242)	0.02	119 (75–206)	129 (94–203)	0.15
Succinate	51 (29–90)	53 (34–99)	0.77	33 (21–54)	29 (20–52)	0.51
Fumarate	**12 (7.1–22)**	**17 (10–29)**	**3.4×10^{-5}**	**9.3 (5.7–18)**	**13 (8.6–22)**	**1.2×10^{-4}**
Malate	**17 (10–36)**	**30 (16–44)**	**2.9×10^{-5}**	**15 (9.0–31)**	**19 (12–39)**	**4.6×10^{-4}**

Variables reaching statistical significance in the discovery and validation substudies are shown in boldface.

[a]Student *t* tests.

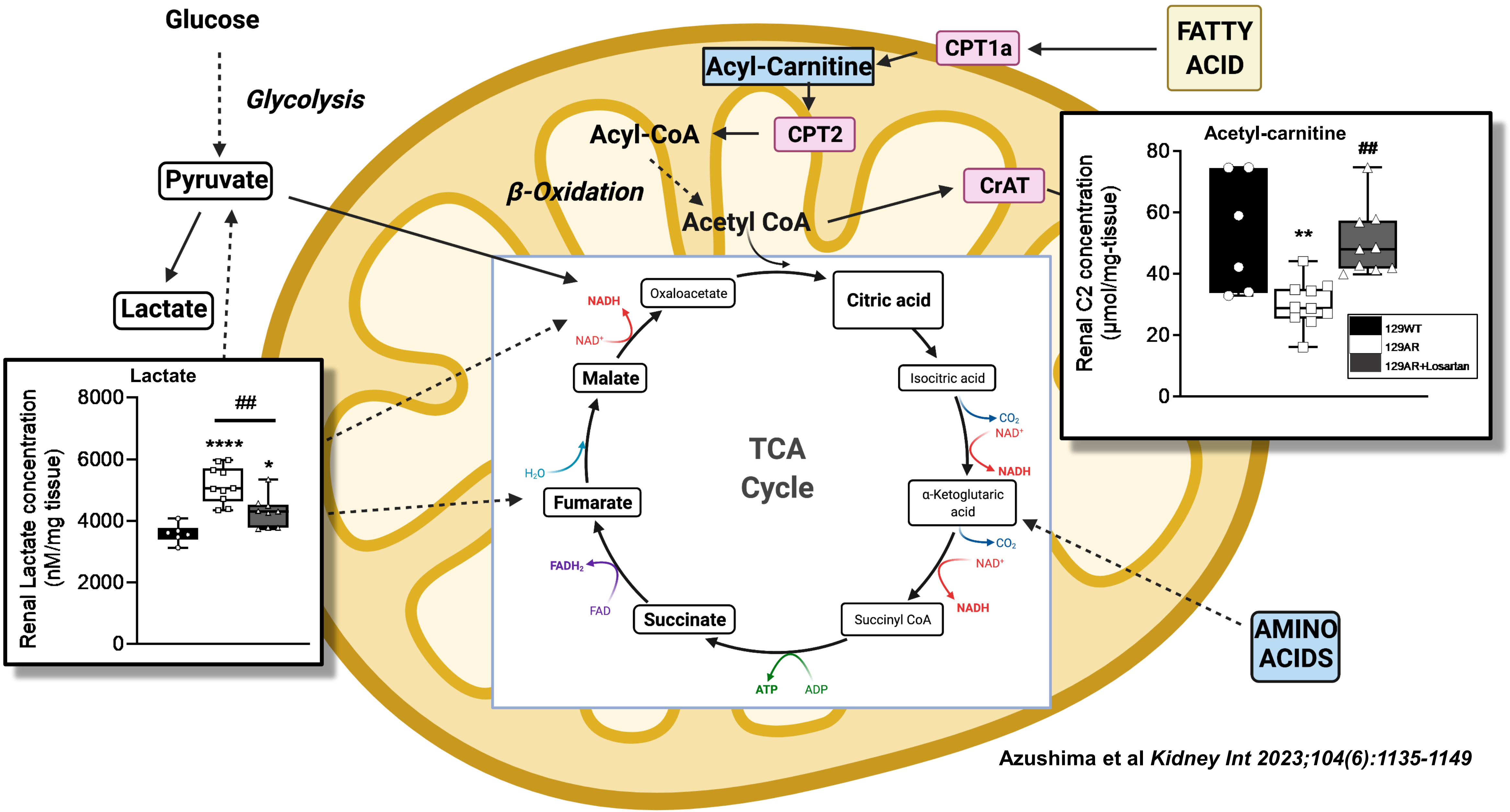
J Clin Endocrinol Metab 103: 4357–4364, 2018

Metabolic Alterations in Kidneys of 129AR Mice



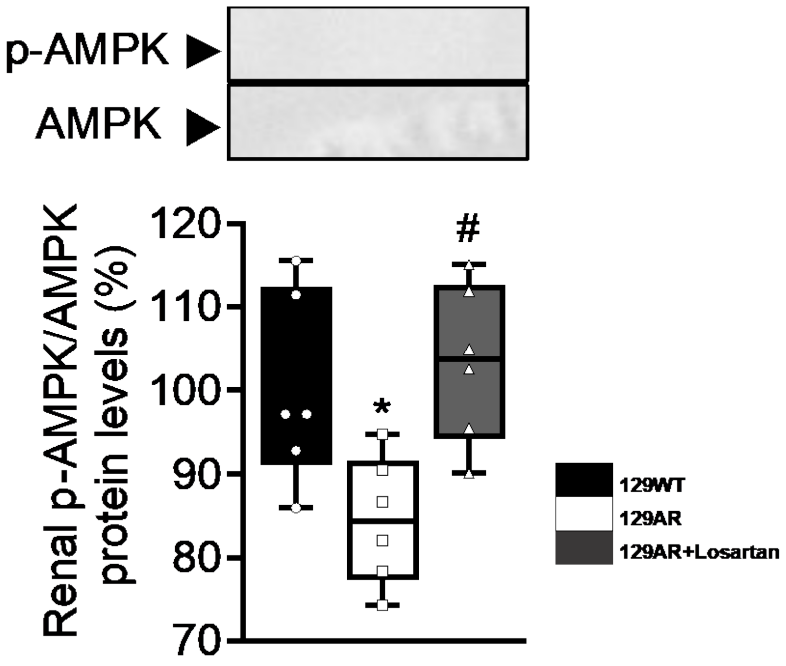
Azushima et al *Kidney Int 2023;104(6):1135-1149*

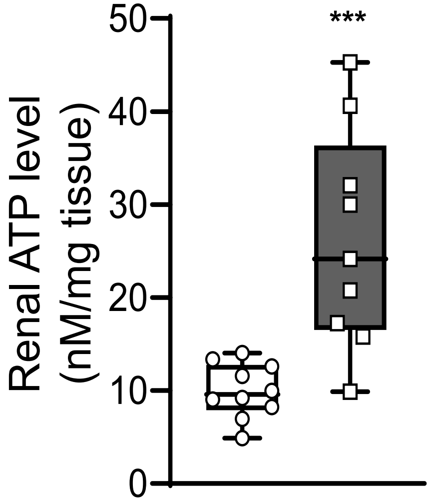
ARB Treatment Corrects Metabolic Abnormalities in Kidneys of 129/



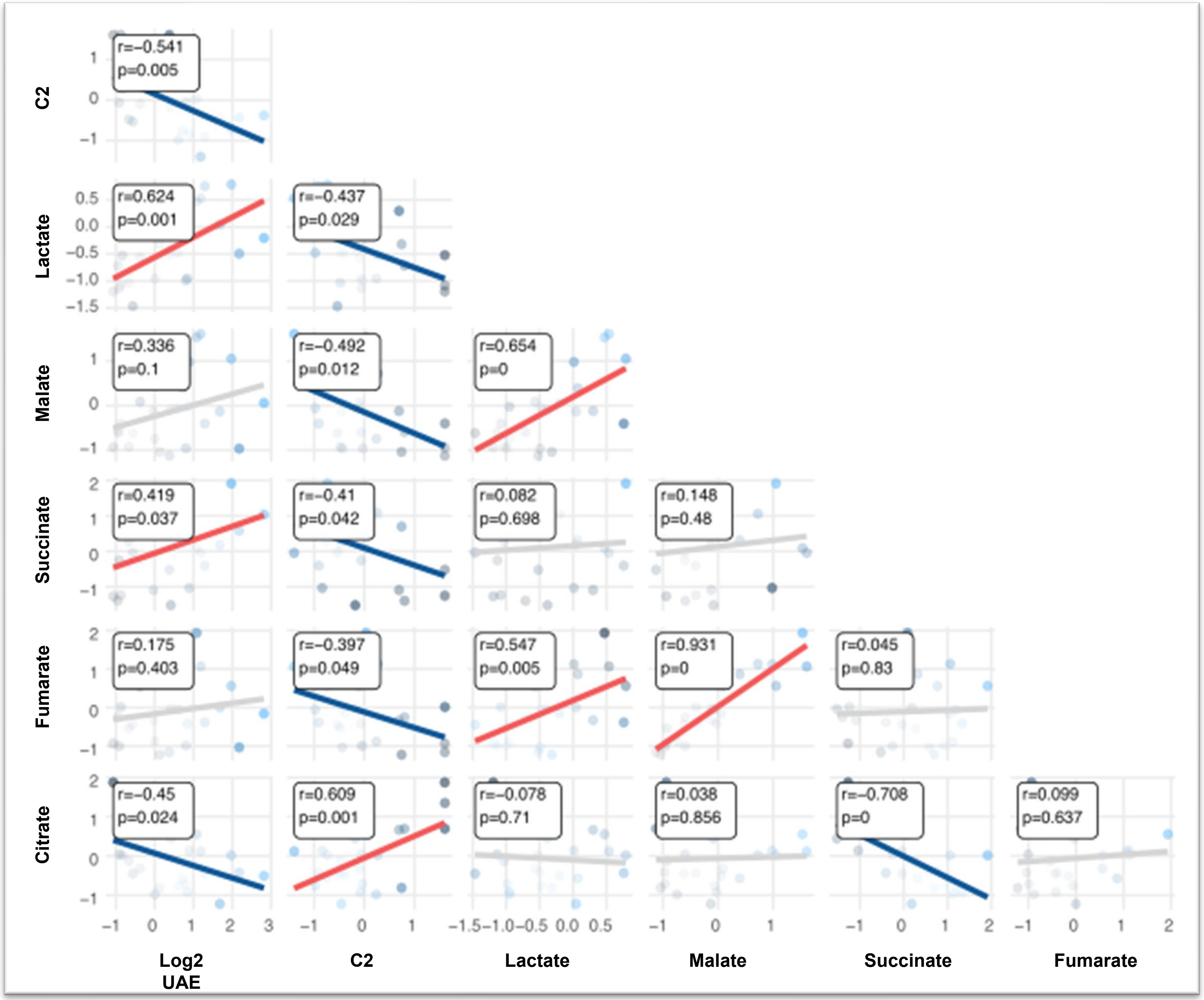
Azushima et al *Kidney Int 2023;104(6):1135-1149*

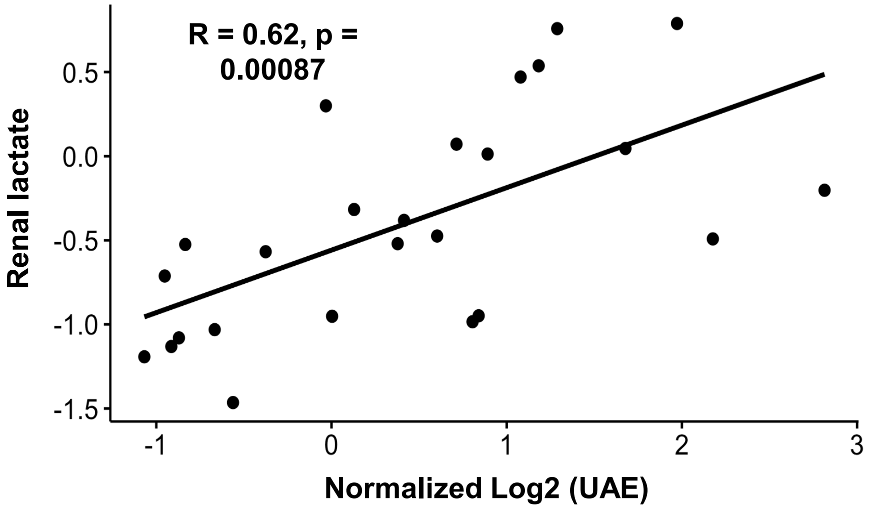
ARB Treatment Corrects Metabolic Abnormalities in Kidneys of 129/





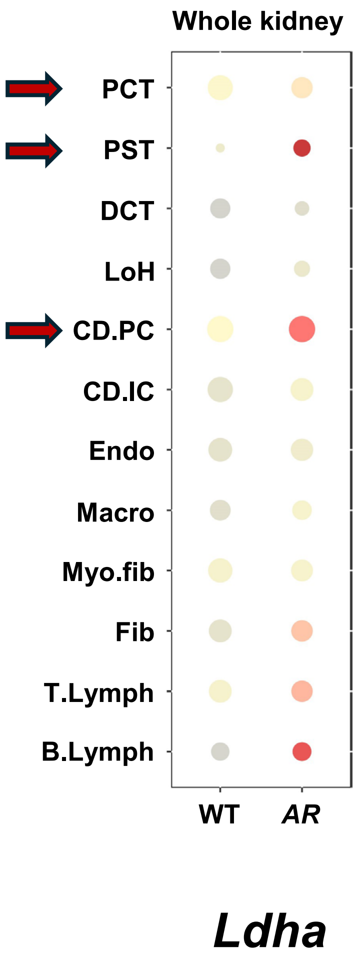
Azushima et al *Kidney Int 2023;104(6):1135-1149*

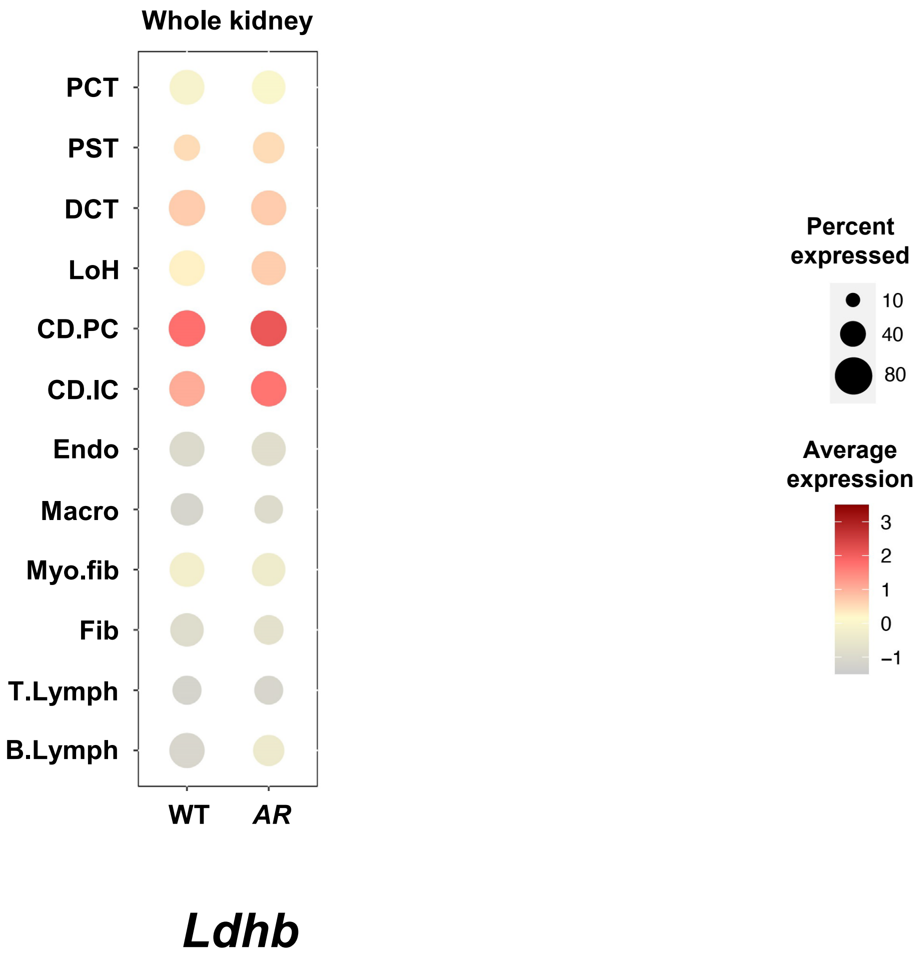




Metabolite Correlations

Mapping Expression of Lactate Dehydrogenase Isoforms in Diabetic Kidney D





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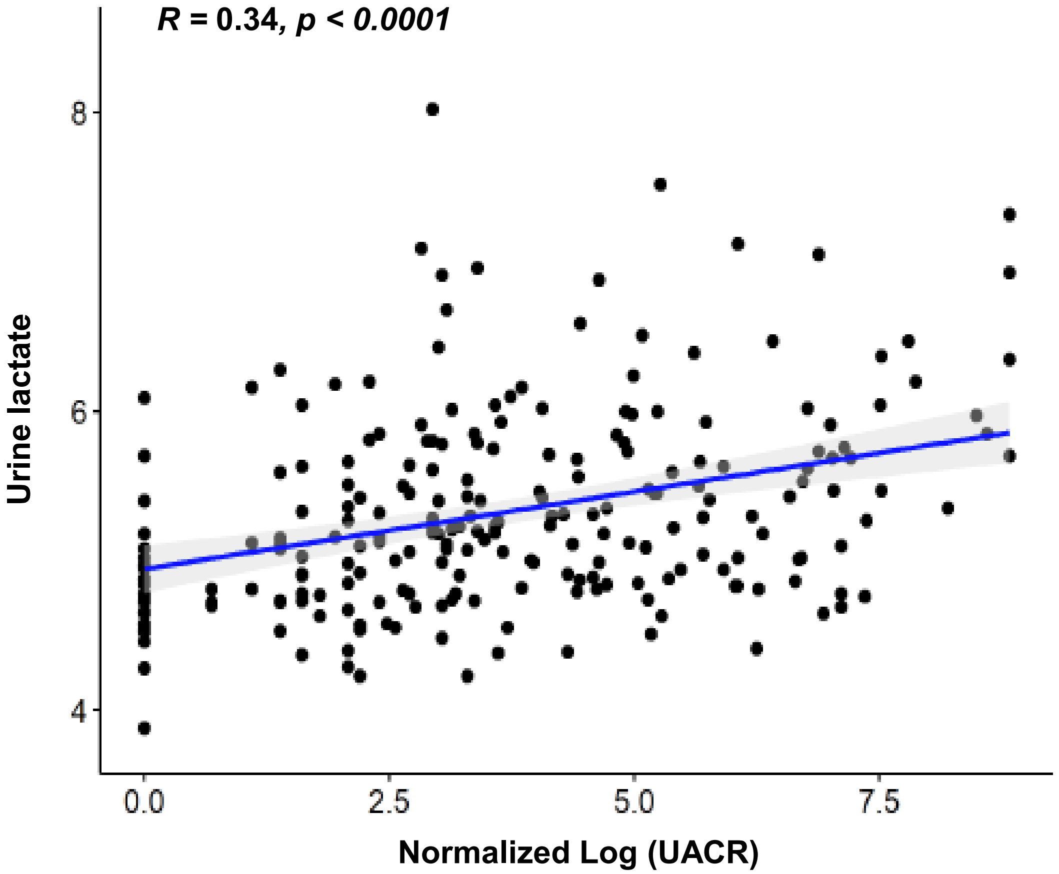
Association Between Urinary Lactate Levels with Albuminuria



R=0.31; [0.16–0.45]; P < 0.001 with RAS blockers;
R=0.49; [0.29–0.67]; P < 0.001 without RAS blockers

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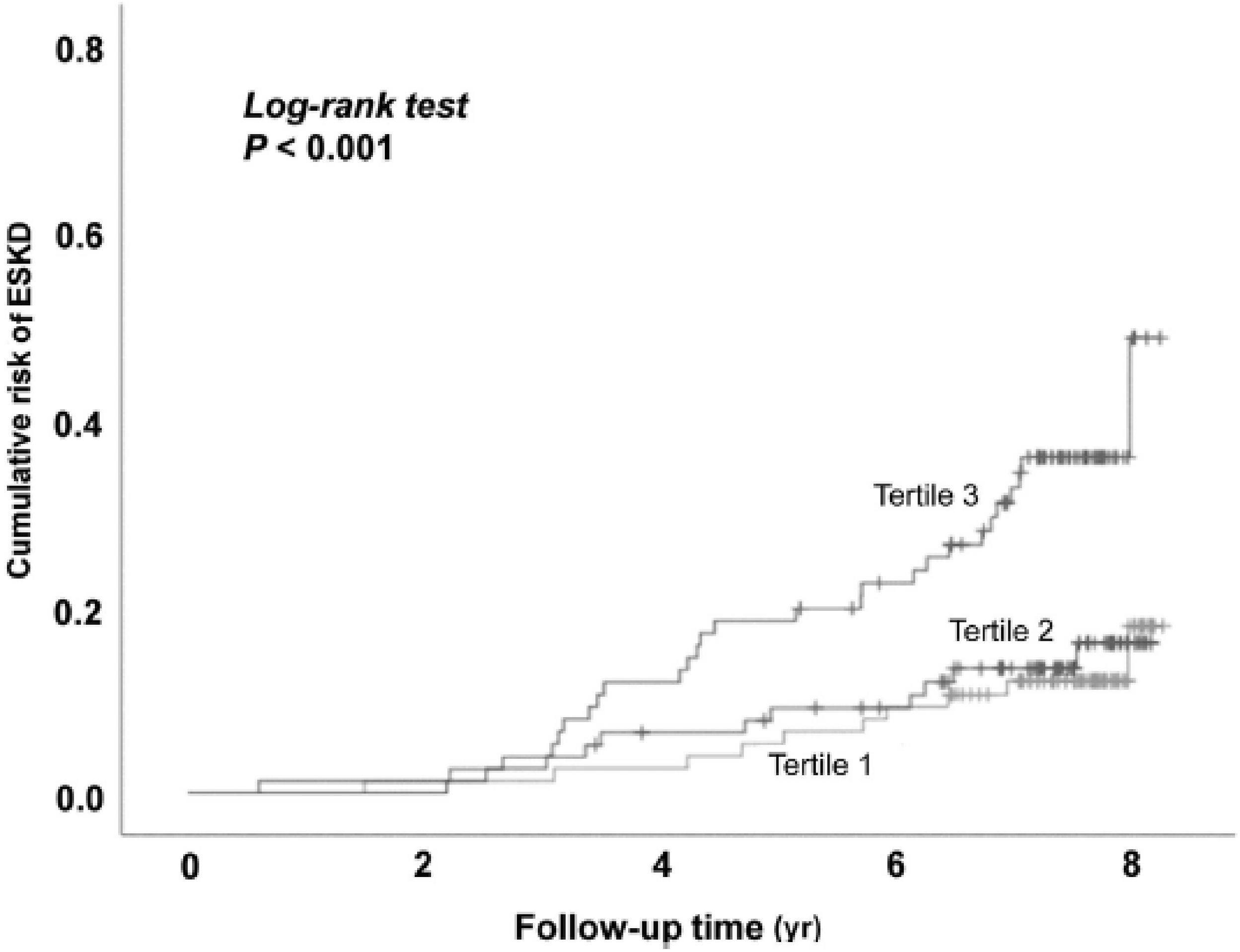
Increased Urinary Lactate Levels are Associated with Risk for ESKD in T2DM



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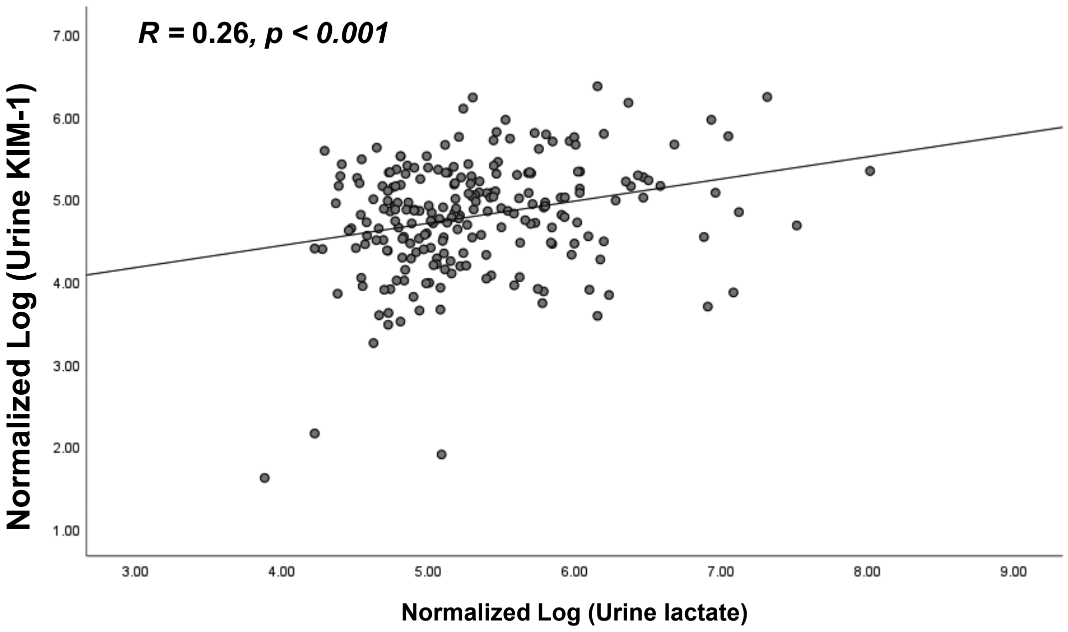
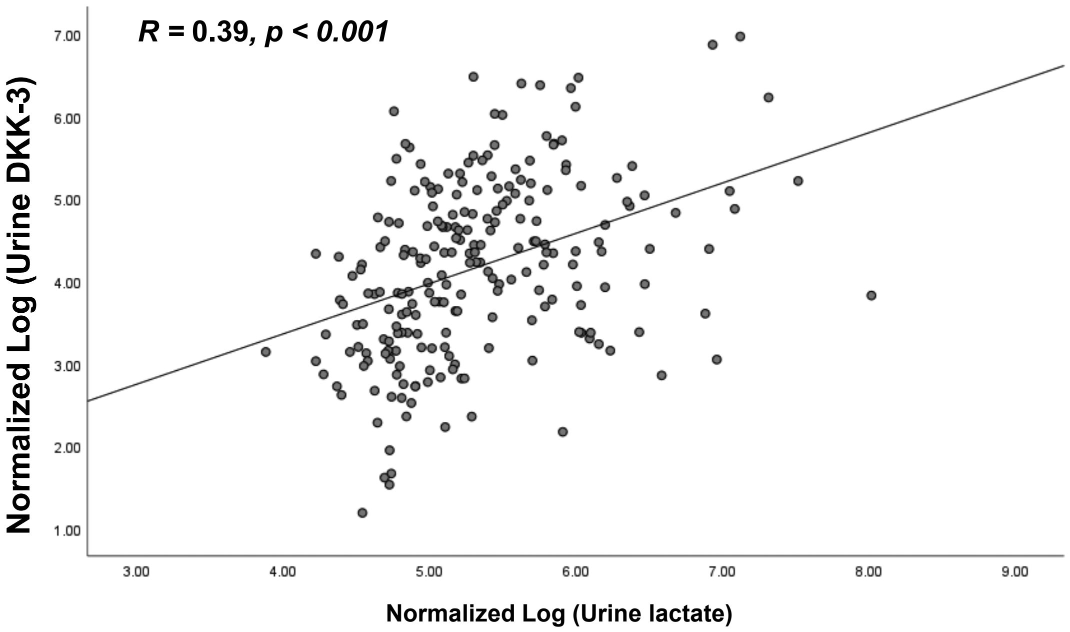
Urinary Lactate Levels Correlate with Markers of Tubular Stress and

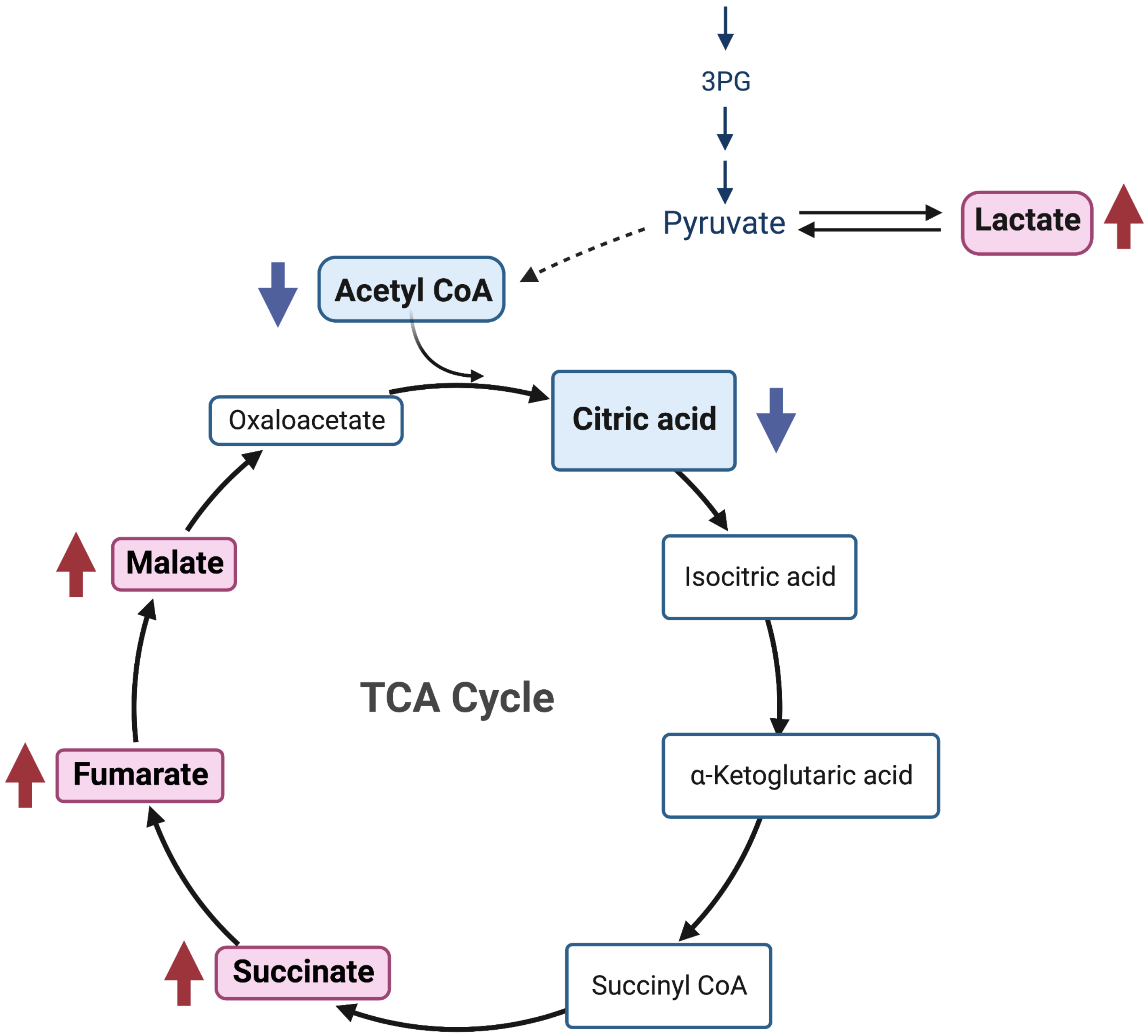


KIM-1



DKK-3

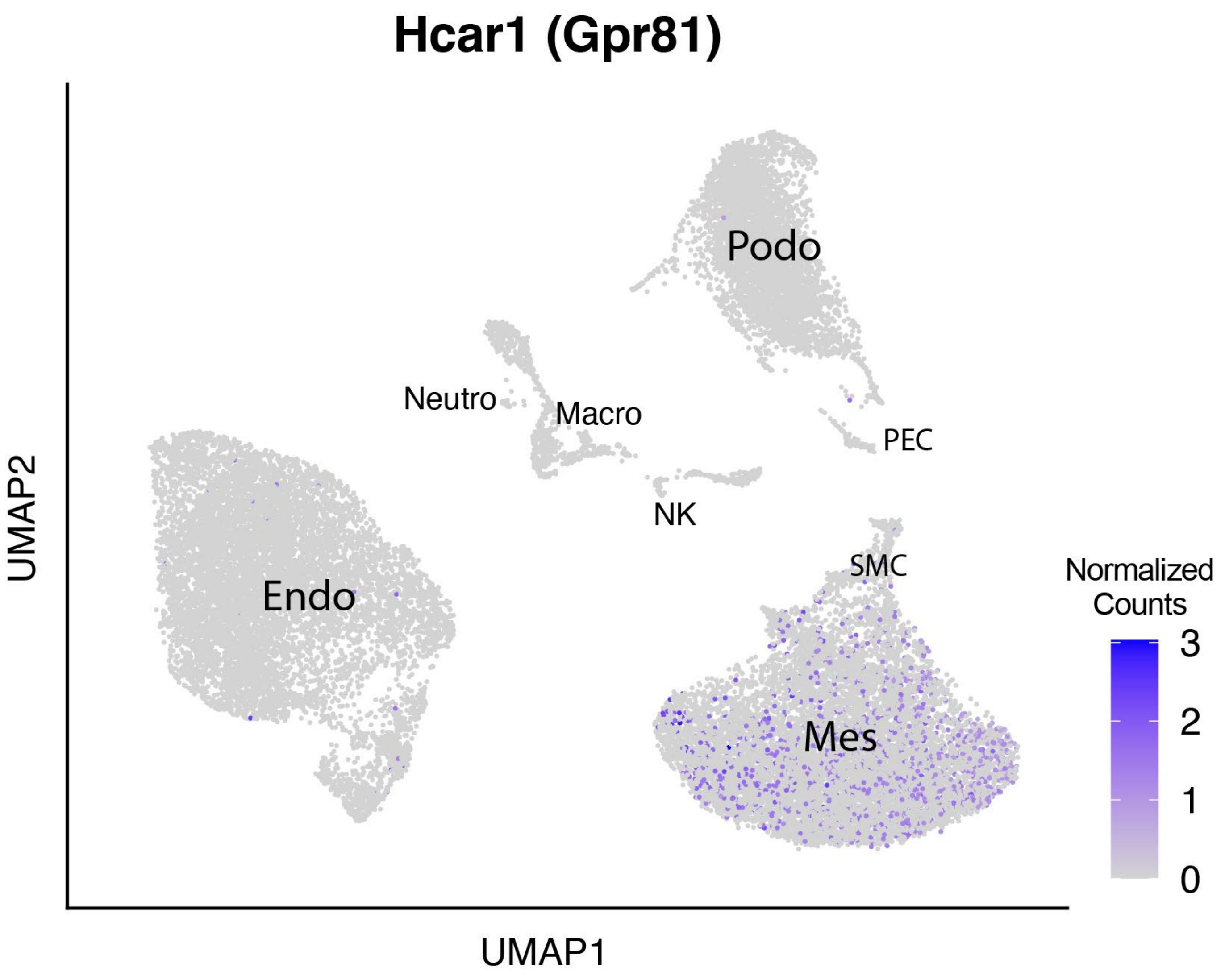
Azushima et al *Kidney Int 2023;104(6):1135-1149*


3PG
Pyruvate
Lactate
Acetyl CoA
Citric acid
Oxaloacetate
Isocitric acid
Malate
TCA Cycle
α-Ketoglutaric acid
Fumarate
Succinate
Succinyl CoA

Summary

- Distinct kidney metabolic defects associated with elevated lactate levels are associated with susceptibility to diabetic kidney disease
- In a human cohort with T2DM, elevated urinary lactate is associated with progression to ESKD
- Increased urinary lactate levels may be a useful biomarker for risk of progressive kidney injury
- The association between abnormal lactate metabolism and albuminuria suggests that lactate may be an indicator of epithelial distress caused by high-grade proteinuria in DN

Expression of GPR81 in Glomerular Mesangial Cells



Acknowledgements

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LIM Su Chi
WANG Jiexun
LIU Jian-Jun

Yokohama City University

Kengo Azushima*


DukeNUS
Medical School
DYNAMO II

Thank you