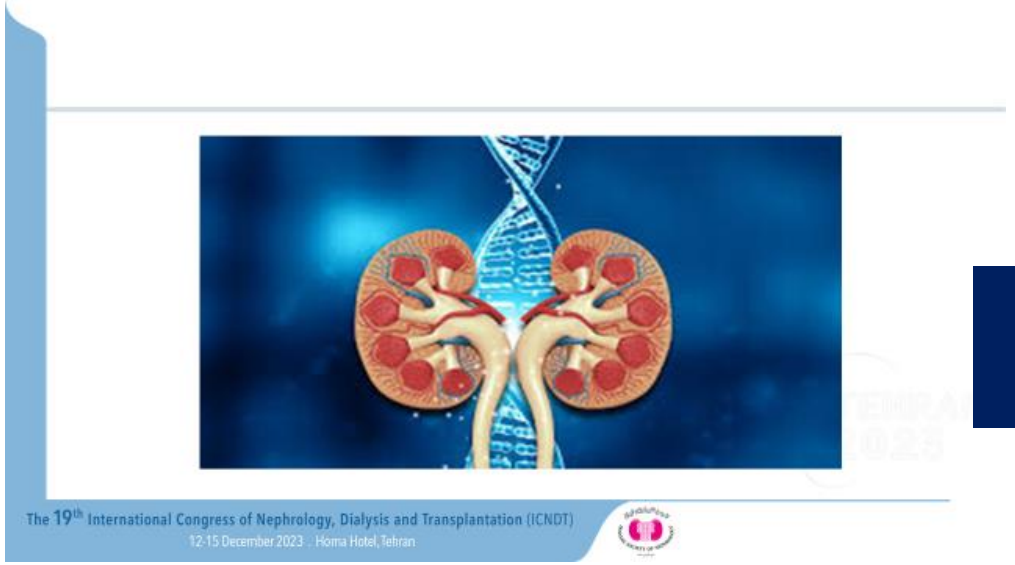
The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023

Homa Hotel, Tehran



Genetic and CKD

Tahereh Malakoutian, M.D
Associate professor of nephrology
Iran University of Medical Science

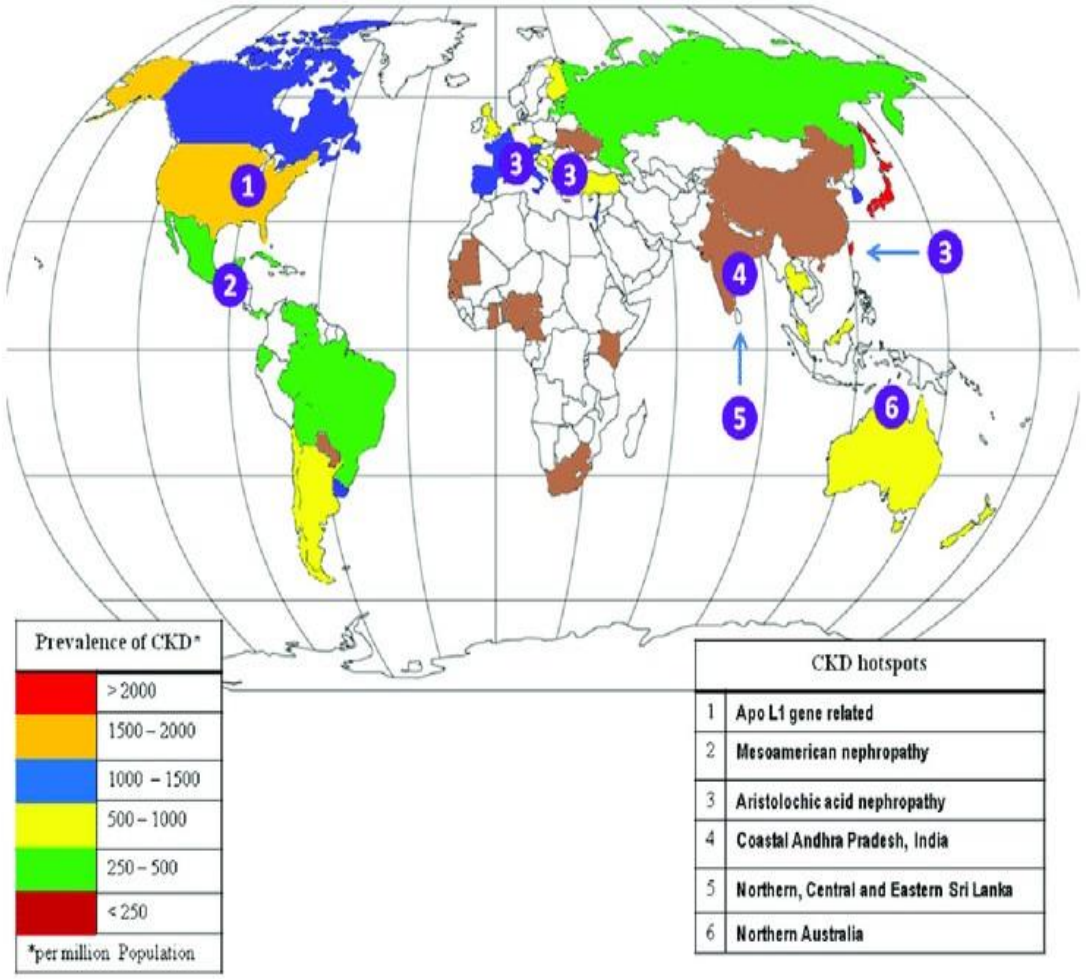
Introduction

850 million people

11-16% of general population

Aging population structure
increased prevalence of D.M, HTN , and obesity.

both genetic and environmental contributions



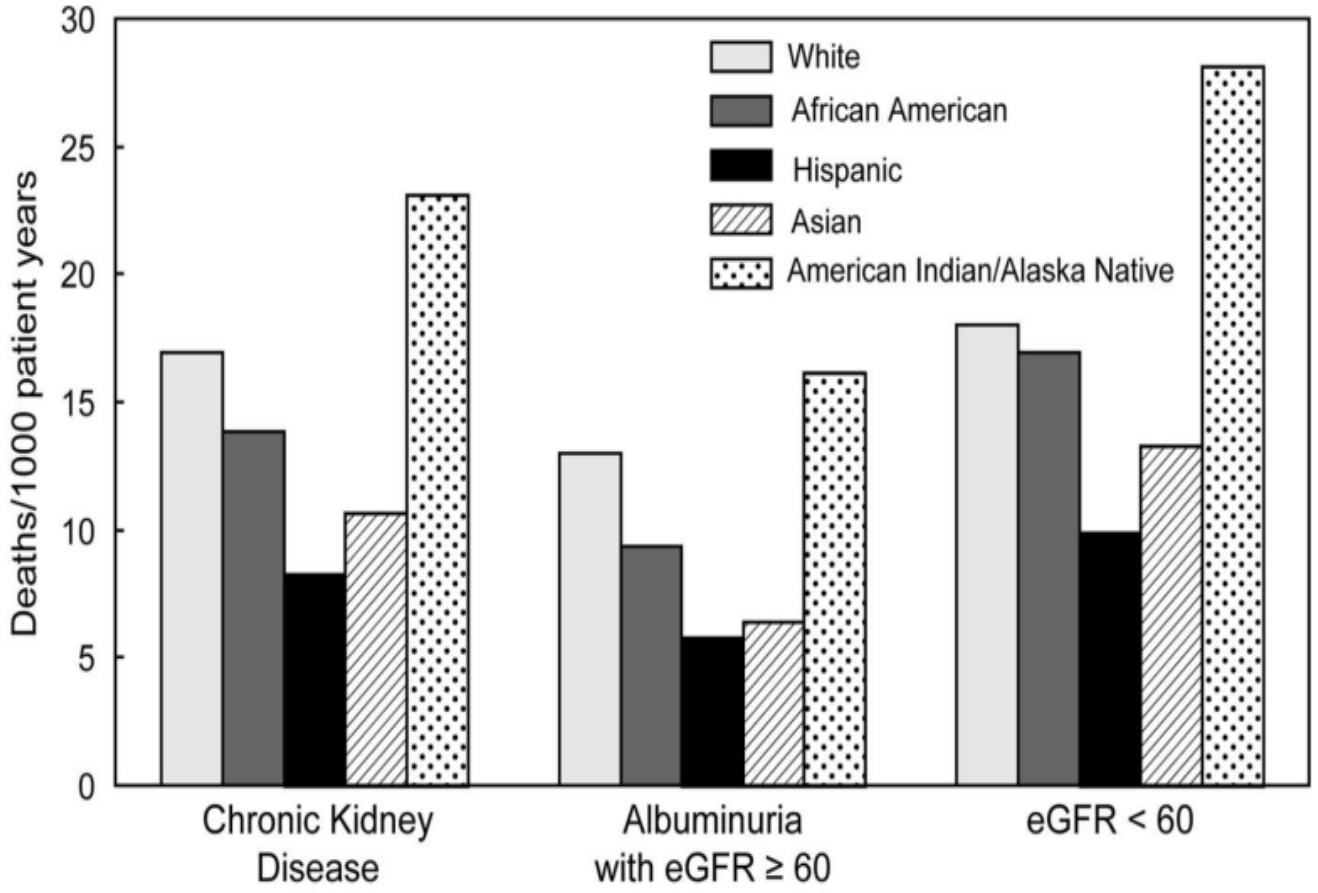
Results from a joint survey by the leading kidney societies : ASN , ISN , and ERA

Rationale for Genetic Studies in Kidney Disease

Familial clustering

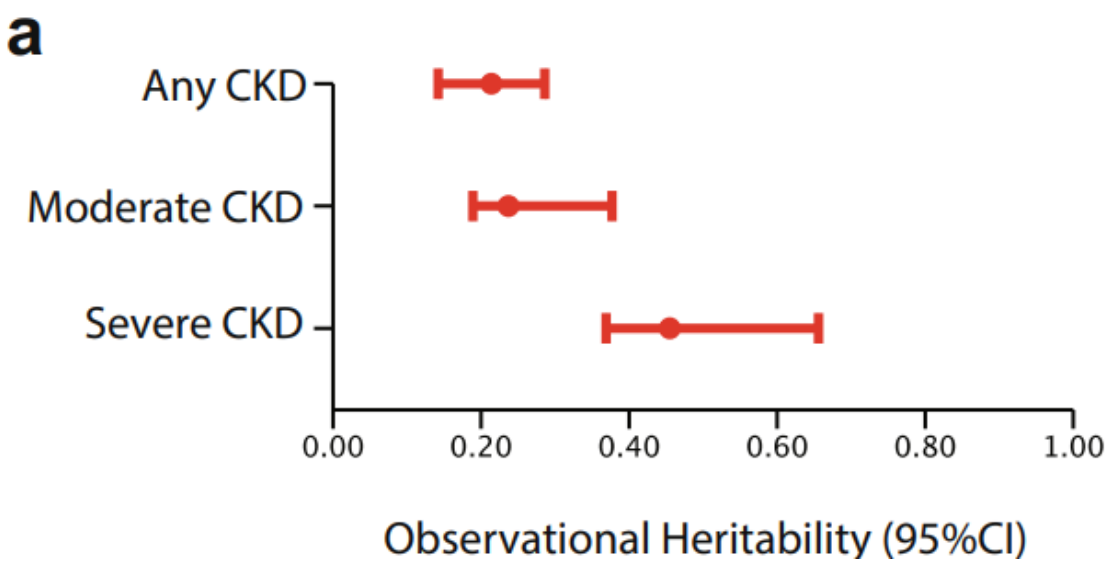
Differing prevalence rate across ethnic groups

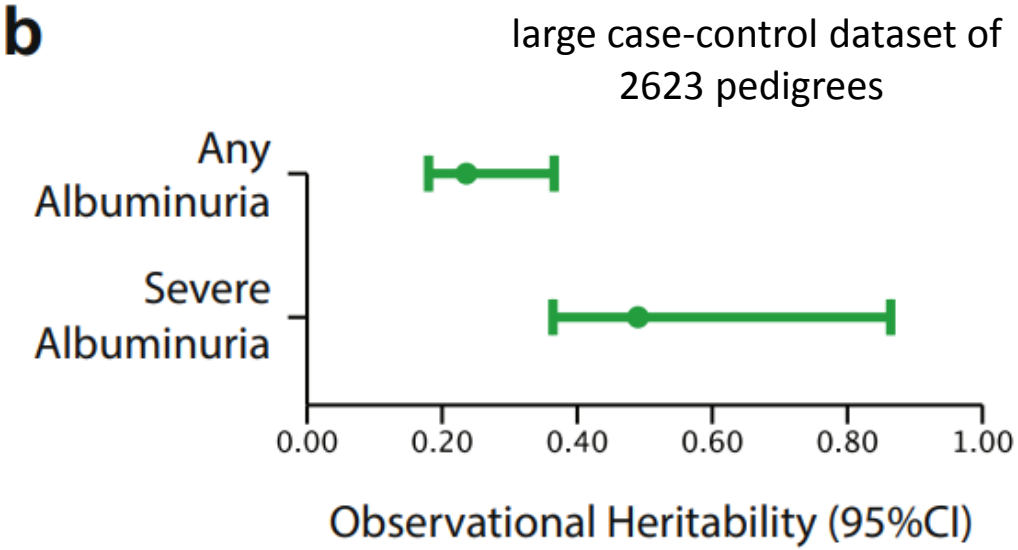
The progression of CKD varies among individuals despite similar etiologies



Stacey E. Jolly. CJASN,2011

Heritability of CKD





large case-control dataset of 2623 pedigrees

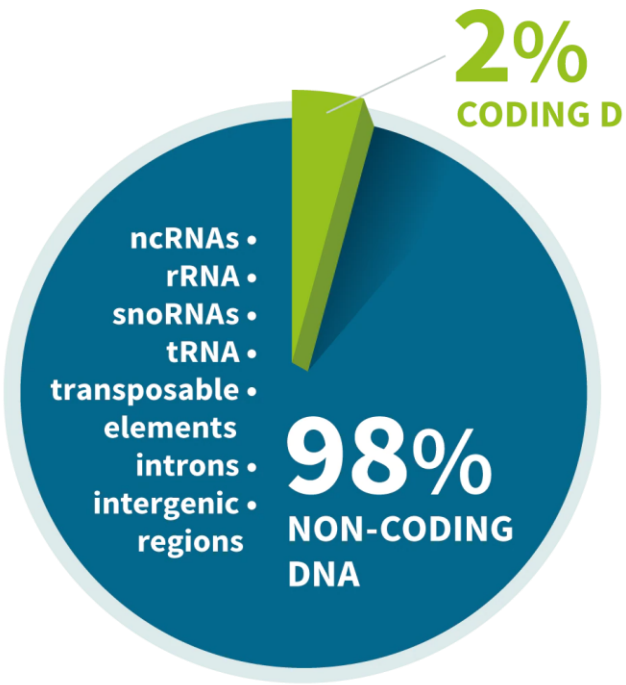
Ning Shang, NPJ, 2021 .

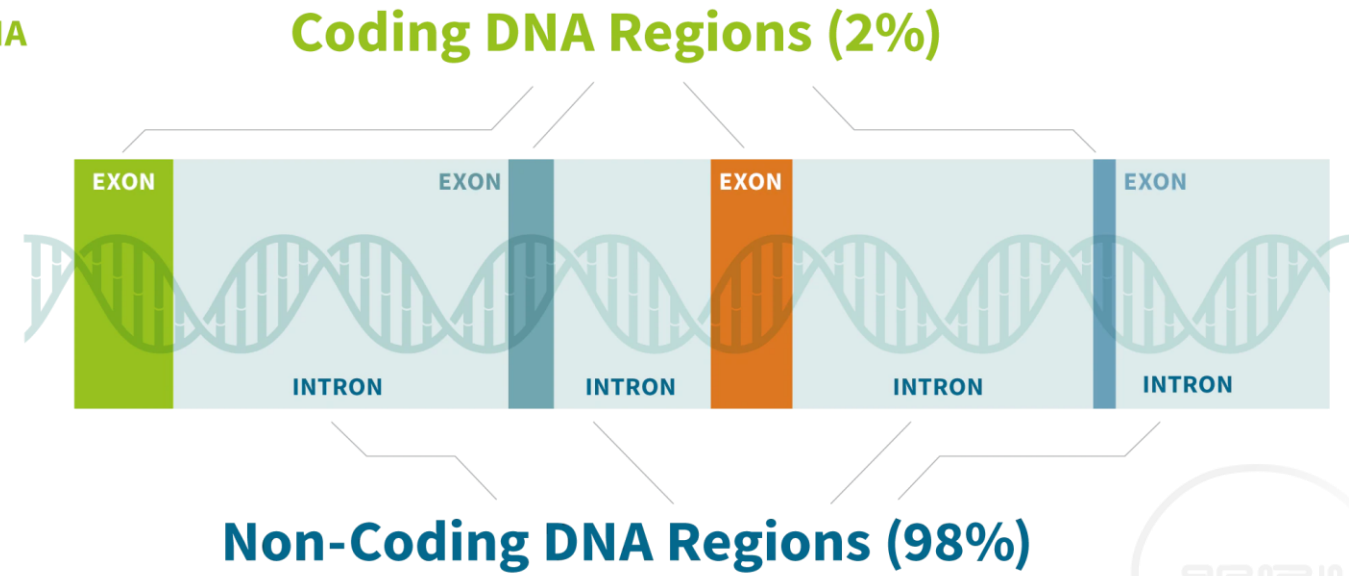
First Author	Risk Factor	Follow-Up (yr)	*n*	Association with Outcomes
Sociodemographic and economic factors				
Ricardo *et al.* (7)	Sex (women versus men)	6.9	3939	↓ Kidney failure[a] risk in women versus men
Fischer *et al.* (9)	Hispanic ethnicity	5.1	3785	Similar kidney failure risk in Hispanic versus non-Hispanic White individuals
Ricardo *et al.* (10)	Nephrologist care	6.6	3855	No significant association
Behavioral factors				
Ricardo *et al.* (11)	Healthy diet, regular physical activity BMI >25 kg/m^2, past/never smoker	4	3006	No significant association ↓ Kidney failure risk in overweight/obese and nonsmokers
He *et al.* (15)	↑ Urinary Na+, K+	15,807 p-y	3939	↑ CKD progression[b] risk
Hu *et al.* (20)	Dietary patterns (DASH, aMED, HEI)	7	2403	↓ CKD progression risk in least versus most adherent tertile
Hu *et al.* (21)	Healthy beverage score	7	2283	↓ CKD progression risk with higher scores
Bundy *et al.* (64)	Tobacco, alcohol, marijuana Heroin	5.5	2288	No significant association ↑ CKD progression risk in users versus nonusers
Schrauben *et al.* (65)	Obese/sedentary pattern in adults <65 yr with diabetes	<3 to >5	5499	↑ CKD progression risk
Ricardo *et al.* (22)	↑ Sleep fragmentation ↓ Sleep duration	4.4	431	↑ eGFR decline and kidney failure risk ↑ eGFR decline
Porter *et al.* (66)	Health-related quality of life	6.2	3837	No significant association
Cedillo-Couvert *et al.* (67)	Medication nonadherence	6	3305	↑ CKD progression risk
Schrauben *et al.* (68)	Self-management behaviors (smoking, poor diet, physical inactivity, and uncontrolled BP)	3	3939	↑ CKD progression risk
Genetic factors				
Parsa *et al.* (26)	APOL1 gene variants	4.4	2955	↑ eGFR decline and CKD progression risk
Parsa *et al.* (28)	SNPs in *LINC00923* (RNA gene expressed in the kidney)	—	3074	↑ eGFR decline and kidney failure risk
Wing *et al.* (69)	DNA methylation pattern	—	40	No significant association
Kelly *et al.* (29)	Renin-angiotensin-aldosterone system genes	—	3013	↑ eGFR decline and CKD progression risk
Cardiovascular factors				
Bansal *et al.* (33)	Atrial fibrillation	5.9	3091	↑ Kidney failure risk
Anderson *et al.* (37)	Time-updated ↑ systolic BP	5.7	3708	↑ Kidney failure risk
Thomas *et al.* (70)	Treatment-resistant HTN	5	3367	↑ CKD progression risk
Townsend *et al.* (45)	↑ Aortic pulse wave velocity	4.1	2795	↑ Kidney failure risk
Grunwald *et al.* (71)	Baseline retinopathy	2.3	1852	No significant association

more than 5000 adults with CKD. Over the past 10 years

Mary Hannan, CJASN , 2021

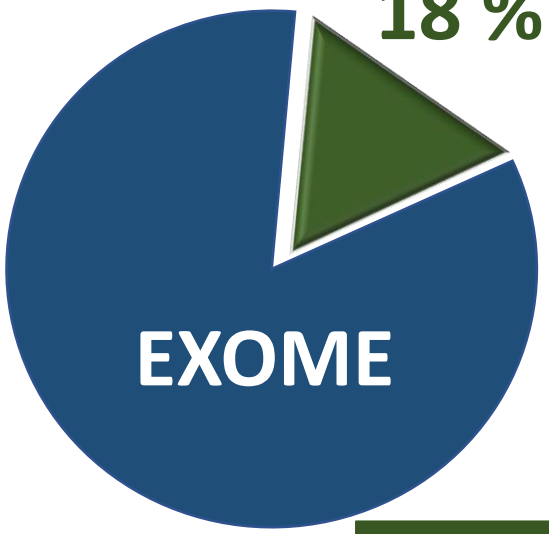
Whole genome-exon





Monogenic / Polygenic Pattern

Monogenic pattern

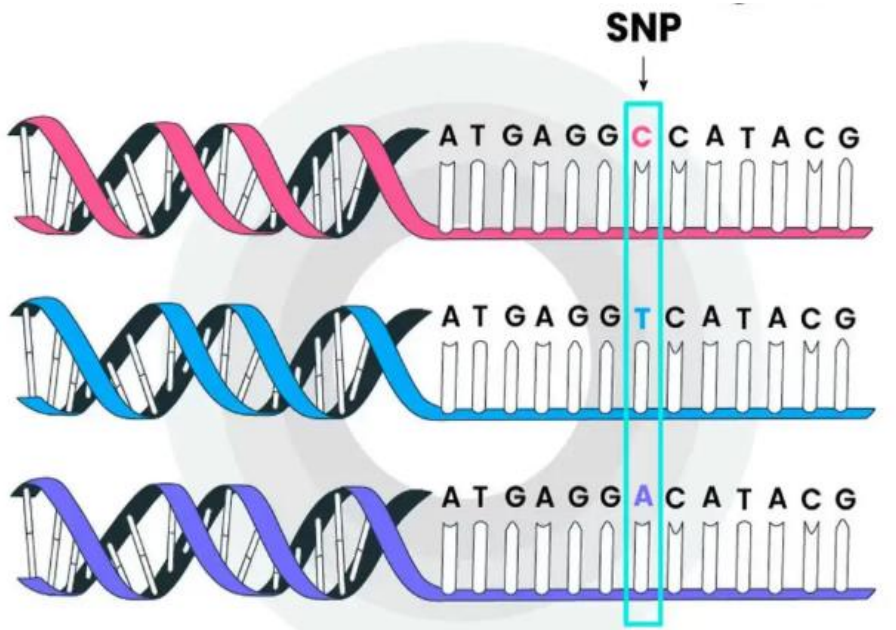


18 % MENDELIAN DISEASE

more than 600 genes

10 –15 % cases of CKD in adults

Polygenic pattern



The genetic contribution to CKD is polygenic, meaning that SNPs in many genes need to be combined to form an effective genetic risk profile to help identify CKD patients with rapid deterioration of kidney function and to identify pre symptomatic individuals who are at higher risk of progressing to CKD

-continued

Genetic causality in CKD

Monogenic disorders

Genotype-phenotype correlation

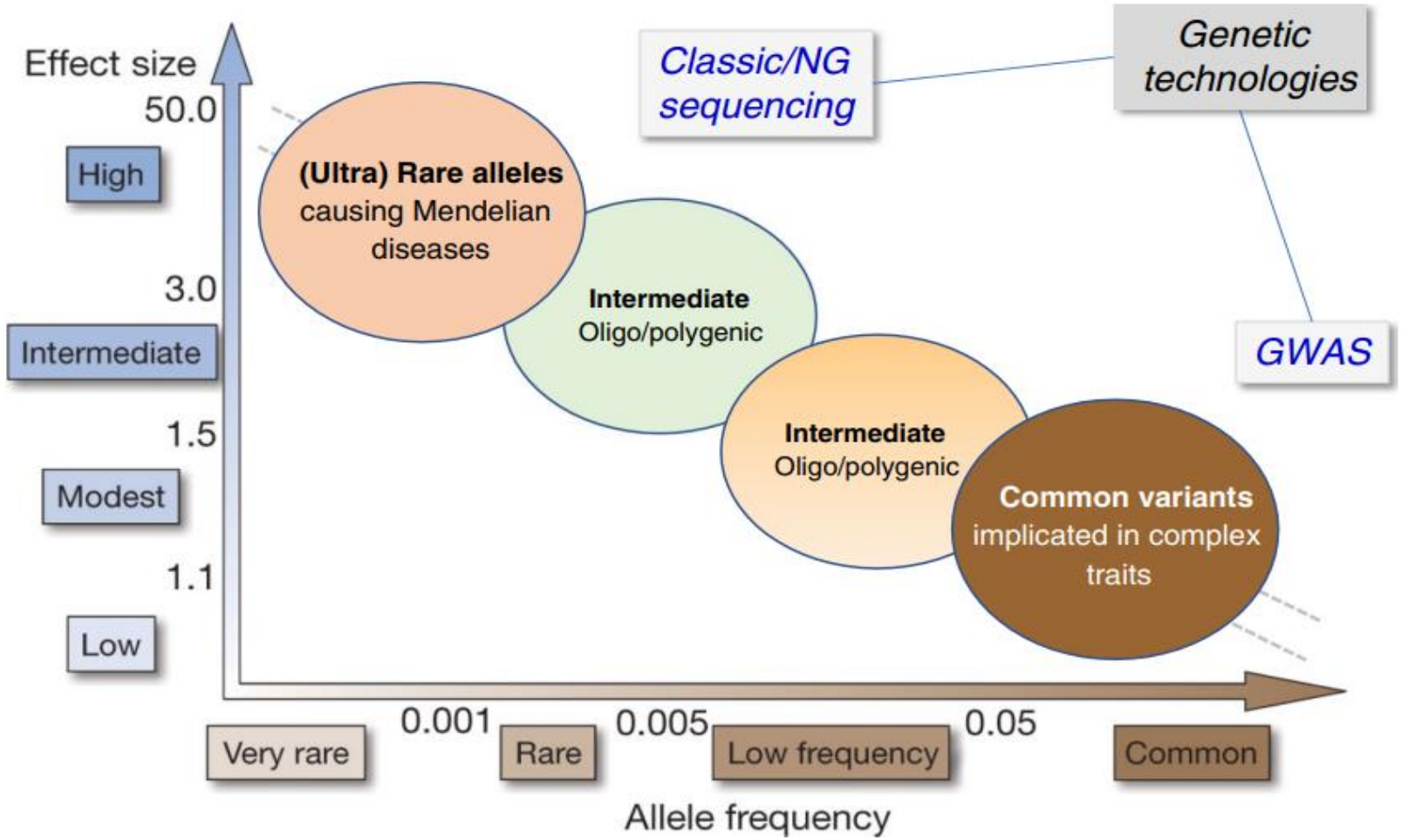
Low penetrance
risk alleles

Conceptually, Mendelian and common complex diseases fall at opposite ends of a spectrum. On one end of this spectrum, there are very rare but very highly penetrant genetic variants in a single gene. The genotype-to-phenotype relationship is strong. Whereas on the other end, there are very common variants at multiple loci in the genome with more subtle effects on phenotype.

Characteristics of monogenic versus complex genetic disease

	MONOGENIC (MENEDELIAN)	POLYGENIC
NUMBER OF VARIANCE RESPONSIBLE	IN ONE PARTICULAR GENE ONLY	IN MULTIPLE GENES AT THE SAME TIME
ALLELE EFFECT	LARGE	INDIVIDUALLY SMALL
INHERITANCE	RECESSIVE OR DOMINANT	POLYGENIC (NON-MENDELIAN)
EFFECT OF ENVIRONMENT	SMALL/NONE	LARGE
Penetrance	High	Low
DISEASE	RARE	COMMON

Genetic architecture of CKD : spectrum of allele frequency and effect size



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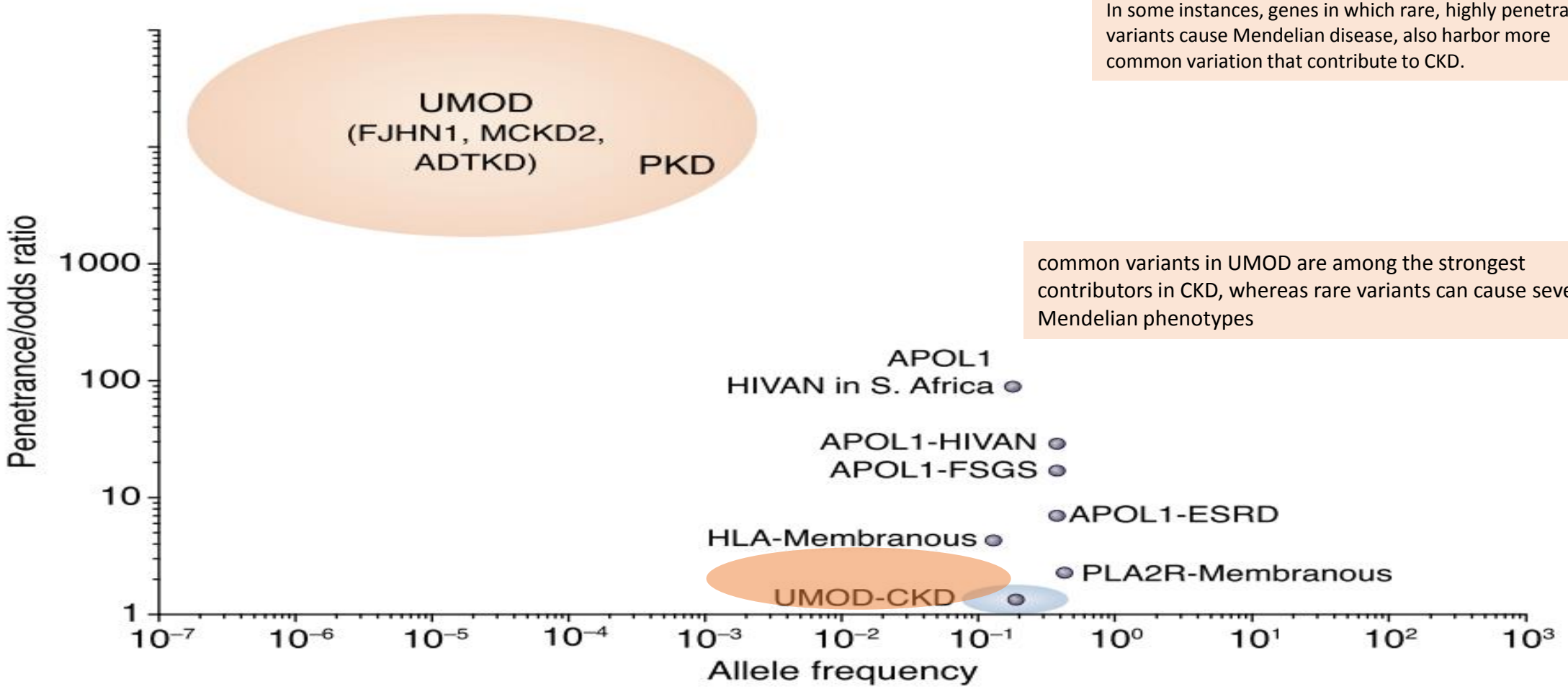
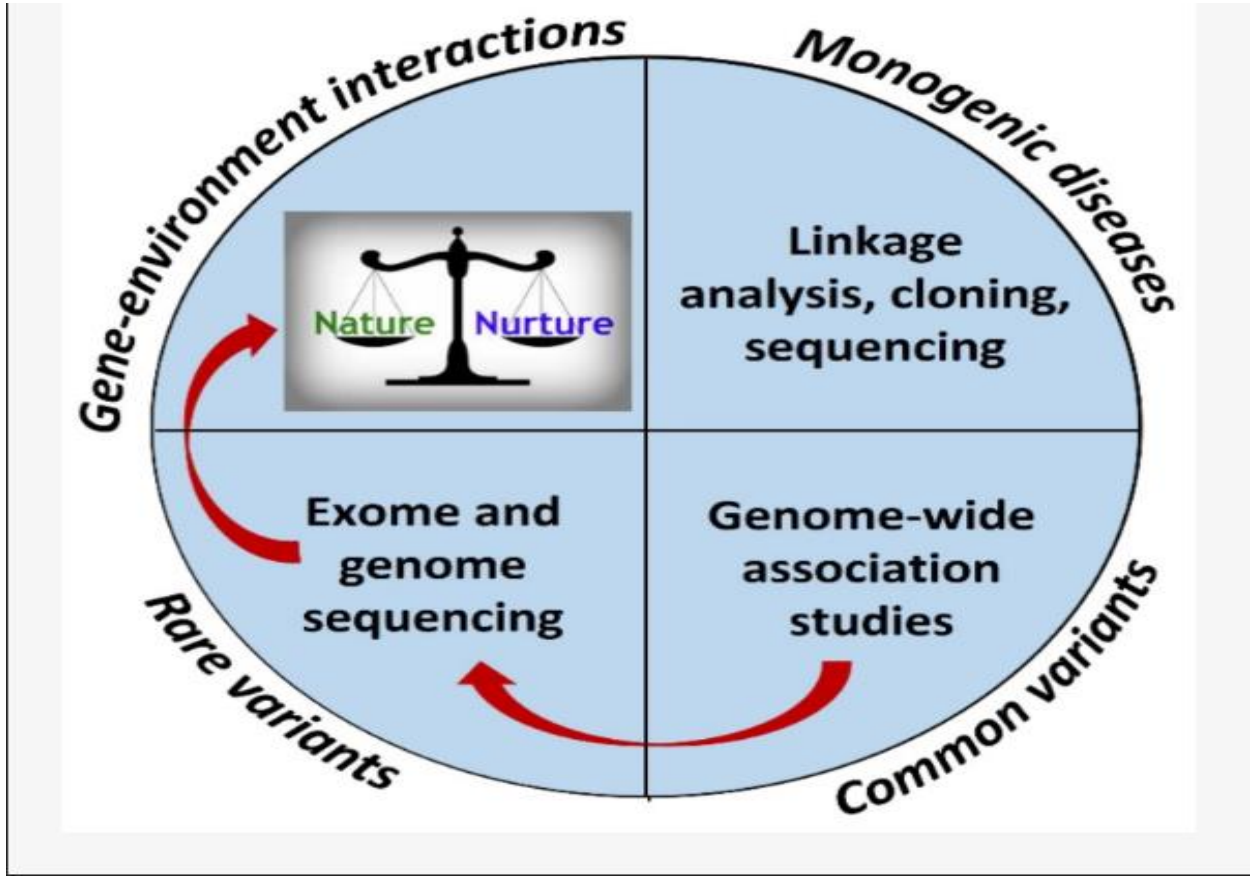
In some instances, genes in which rare, highly penetrant variants cause Mendelian disease, also harbor more common variation that contribute to CKD.

common variants in UMOD are among the strongest contributors in CKD, whereas rare variants can cause severe Mendelian phenotypes



Genetic Studies in CKD



NGS approaches

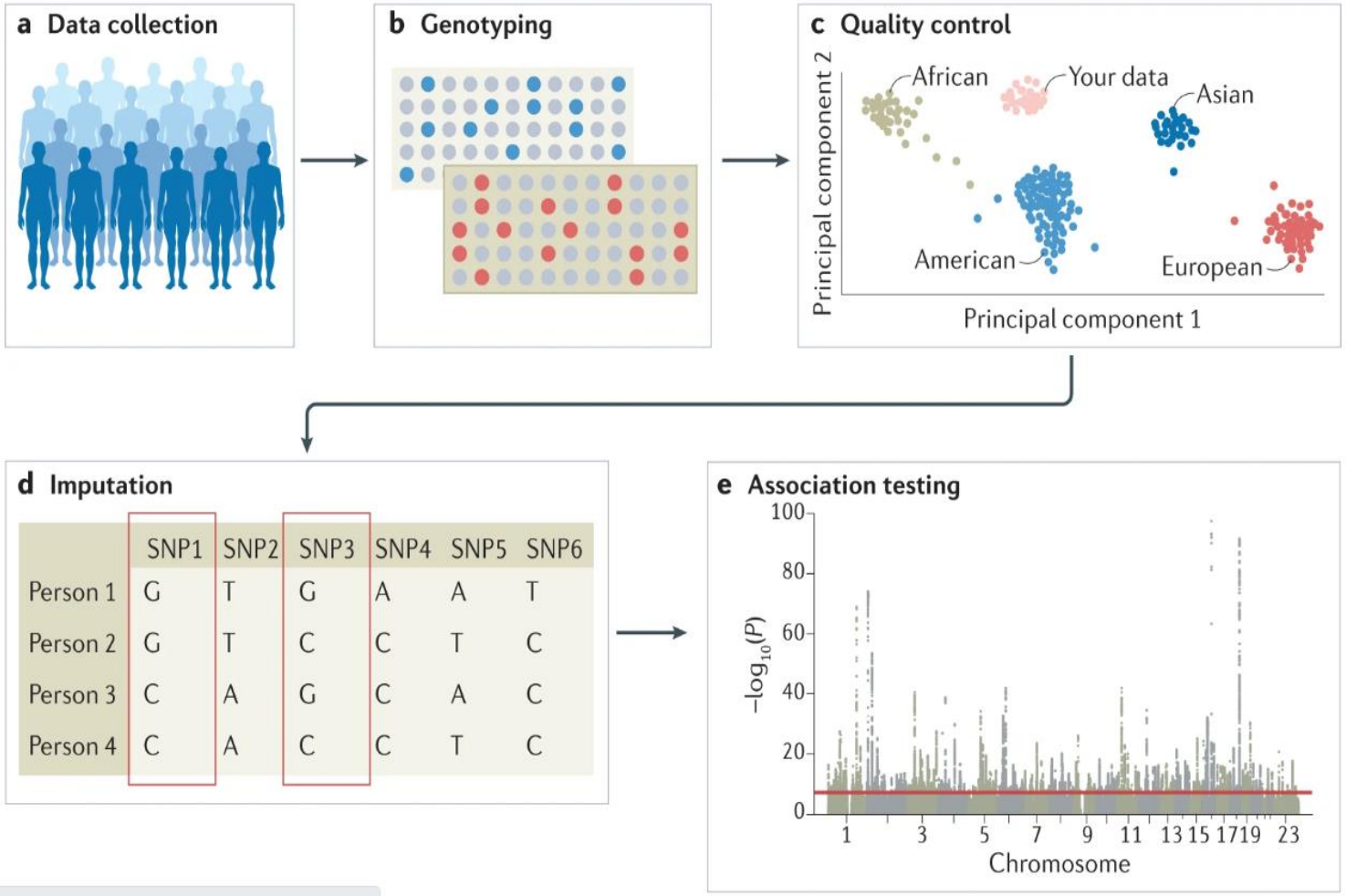
Targeted gene panel (coding regions of disease-specific genes)

Exome sequencing (nearly all exons in the genome)

Genome sequencing (all genome)

Markku laasko,Nutrients 2022

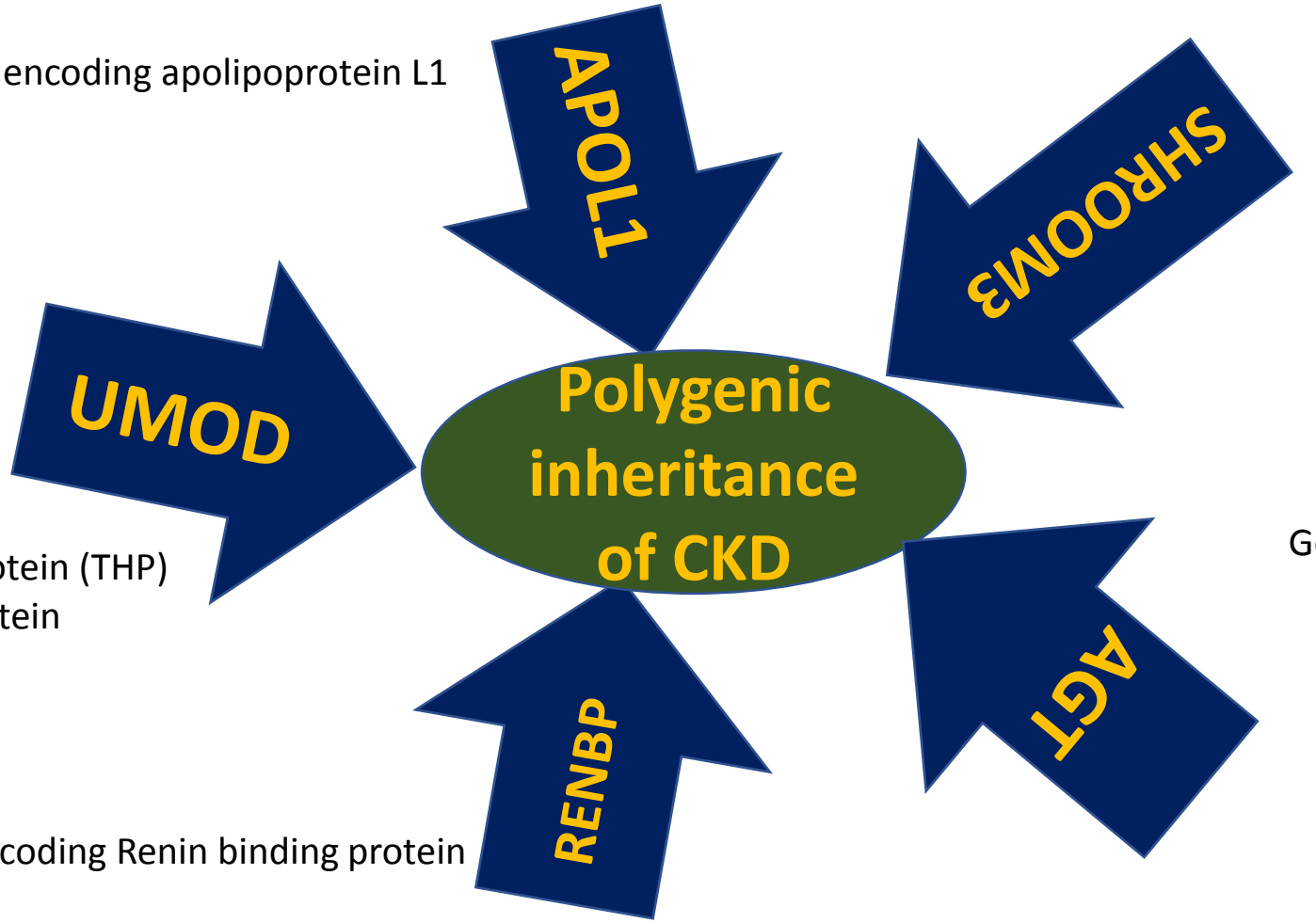
Overview of steps for conducting GWAS



GWASs typically genotype millions of SNPs across many genomes to find those statistically associated with a specific trait (for example eGFR, albuminuria) or disease

GWAS aim to identify associations of genotypes with phenotypes by testing for differences in the allele frequency of genetic variants between individuals who are ancestrally similar but differ phenotypically. GWAS typically report blocks of correlated SNPs that all show a statistically significant association with the trait of interest, known as genomic risk loci.

GWAS for kidney function



Gene encoding apolipoprotein L1

Gene encoding Protein shroom3

Tamm–Horsfall protein (THP)
or uromodulin protein

Gene encoding pre-angiotensinogen

Gene encoding Renin binding protein

The role of renin–angiotensin–aldosterone system genes in the progression of chronic kidney disease: findings from the Chronic Renal Insufficiency Cohort (CRIC) study

Tanika N. Kelly[1], Dominic Raj[2], Mahboob Rahman[3], Matthias Kretzler[4], Radhakrishna R. Kallem[5], Ana C. Ricardo[6], Sylvia E. Rosas[7], Kaixiang Tao[8], Dawei Xie[8], Lotuce Lee Hamm[9] and Jiang He[1,9] on behalf of the CRIC Study Investigators*

[1]School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA 70112, USA, [2]Medical Faculty Associates, George Washington University, Washington, DC 20037, USA, [3]University Hospitals Case Medical Center, Case Western Reserve University, Louis Stokes Cleveland VA Medical Center, Cleveland, OH 44106, USA, [4]University of Michigan, Ann Arbor, MI 48109, USA, [5]University of Pennsylvania, Translational Research Center, Philadelphia, PA 19104, USA, [6]University of Illinois at Chicago, Chicago, IL 60612, USA, [7]Joslin Diabetes Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA, [8]The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA and [9]Tulane University School of Medicine, New Orleans, LA 70112, USA

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*A list of CRIC Study Investigators is given in the acknowledgements section.

In this study , the association between RAAS variants and CKD progression was examined among 3000 participants. 1523 white and 1490 black subjects were genotyped for 490 SNP in 12 RAAS genes Between 2003 and 2008

CKD progression phenotypes included decline in eGFR over time and the occurrence of a renal disease event, defined as incident ESRD or a doubling of the serum creatinine level from baseline

They identified strong gene- and pathway-based associations with CKD progression.

Gene-based associations of RAAS variants and renal event among CRIC study participants

HGNC symbol	*k*	Model 1[a]	Model 2[b]	Model 3[c]
Whites				
RAAS pathway	254	$<1.00 \times 10^{-6}$ [d]	1.10×10^{-5} [d]	5.16×10^{-4} [d]
REN	23	0.07	0.59	0.77
HSD11B1	10	0.24	0.34	0.56
AGT	42	$<1.00 \times 10^{-6}$ [d]	$<1.00 \times 10^{-6}$ [d]	$<1.00 \times 10^{-6}$ [d]
AGTR1	44	0.87	0.56	0.73
NR3C2	71	0.53	0.47	0.72
CYP11B1	3	0.20	0.15	0.26
CYP11B2	7	1.00×10^{-6} [d]	1.60×10^{-5} [d]	0.33
ACE	24	0.45	0.77	0.55
ACE2	17	0.61	0.33	0.60
AGTR2	8	0.43	0.64	0.004
RENBP	5	1.70×10^{-5} [d]	0.31	0.28

A total of 1523 white and 1490 black subjects were genotyped for 490 SNPs in 12 RAAS genes

The AGT and RENBP genes were consistently associated with risk of renal events in separate analyses of white and black participants (both $P < 1.00 \times 10-6$).

Tanika N, N D T (2015)

-Continued

Blacks				
RAAS pathway	375	$<1.00 \times 10^{-6}$ [d]	$<1.00 \times 10^{-6}$ [d]	$<1.00 \times 10^{-6}$ [d]
REN	38	0.97	0.78	0.63
HSD11B1	11	0.61	0.22	0.03
AGT	47	$<1.00 \times 10^{-6}$ [d]	0.001[d]	1.00×10^{-6} [d]
AGTR1	73	0.15	0.45	0.60
NR3C2	88	0.80	0.59	0.64
CYP11B1	3	0.04	0.03	0.20
CYP11B2	7	0.37	0.35	0.48
ACE	42	0.43	0.06	0.49
ACE2	43	$<1.00 \times 10^{-6}$ [d]	$<1.00 \times 10^{-6}$ [d]	$<1.00 \times 10^{-6}$ [d]
AGTR2	13	0.36	0.33	0.58
RENBP	9	2.20×10^{-5} [d]	0.05	0.006

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 5, 2013 VOL. 369 NO. 23

APOL1 Risk Variants, Race, and Progression of Chronic Kidney Disease

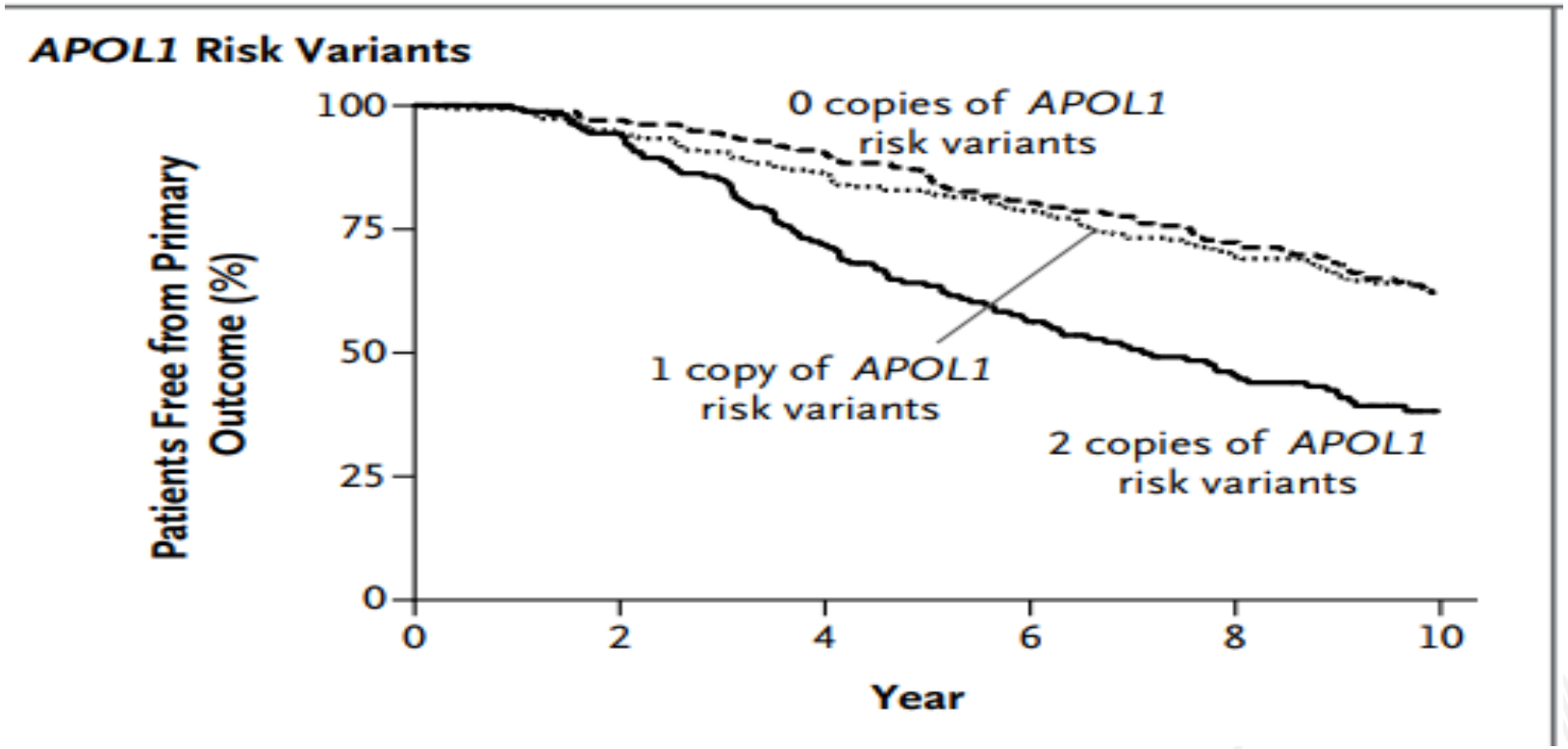
they examined the effects of APOL1 variants on CKD progression

Afshin Parsa, M.D., M.P.H., W.H. Linda Kao, Ph.D., Dawei Xie, Ph.D., Brad C. Astor, Ph.D., M.P.H., Man Li, M.S., Chi-yuan Hsu, M.D., Harold I. Feldman, M.D., Rulan S. Parekh, M.D., John W. Kusek, Ph.D., Tom H. Greene, Ph.D., Jeffrey C. Fink, M.D., Amanda H. Anderson, Ph.D., Michael J. Choi, M.D., Jackson T. Wright, Jr., M.D., Ph.D., James P. Lash, M.D., Barry I. Freedman, M.D., Akinlolu Ojo, M.D., Ph.D., Cheryl A. Winkler, Ph.D., Dominic S. Raj, M.D., Jeffrey B. Kopp, M.D., Jiang He, M.D., Ph.D., Nancy G. Jensvold, M.P.H., Kaixiang Tao, Ph.D., Michael S. Lipkowitz, M.D., and Lawrence J. Appel, M.D., M.P.H., for the AASK and CRIC Study Investigators*

Role of APOL1 risk variants on progression of CKD

from2003 through 2008, a total of 3288 black patients and white patients with an eGFR of 20 to 70 ml/min were enrolled

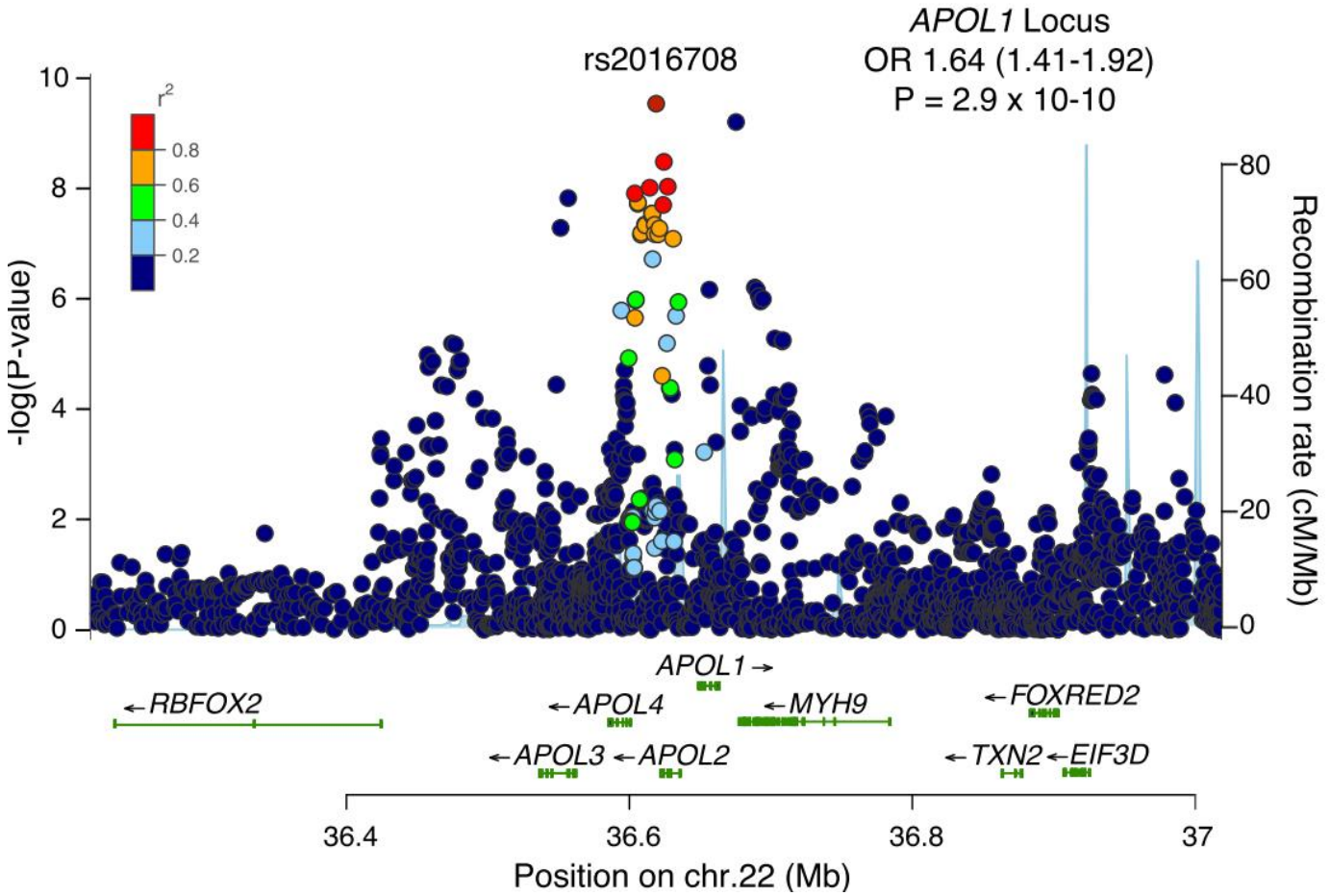
hazard ratio, 2.03 P<0.001



Patients with 2 copies of the APOL1 risk variants were about twice as likely to progress to the composite renal outcome (ESRD or a decline in the eGFR of at least 50% from baseline) as was the reference group

Afshin Parsa, n engl j med , 2013

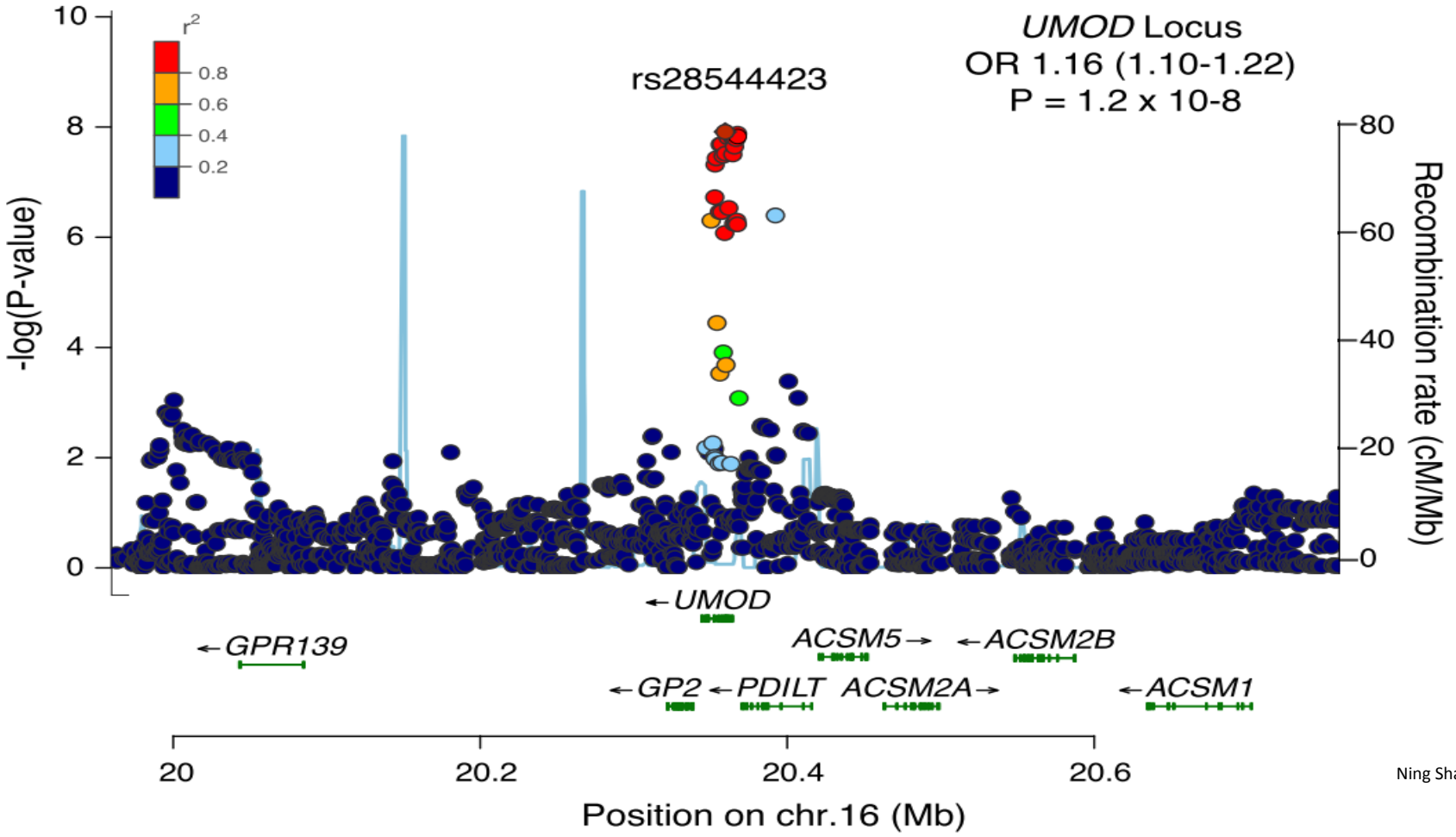
APOL1 locus



Another GWAS pedigree-based analyses in 2021, showed a genome-wide significant signal at the known APOL1 locus (rs2016708, OR = 1.64, 95% CI: 1.41–1.92, P = 2.9 × 10−10) among African ancestry

Ning Shang, NPJ, 2021

Uromodulin locus

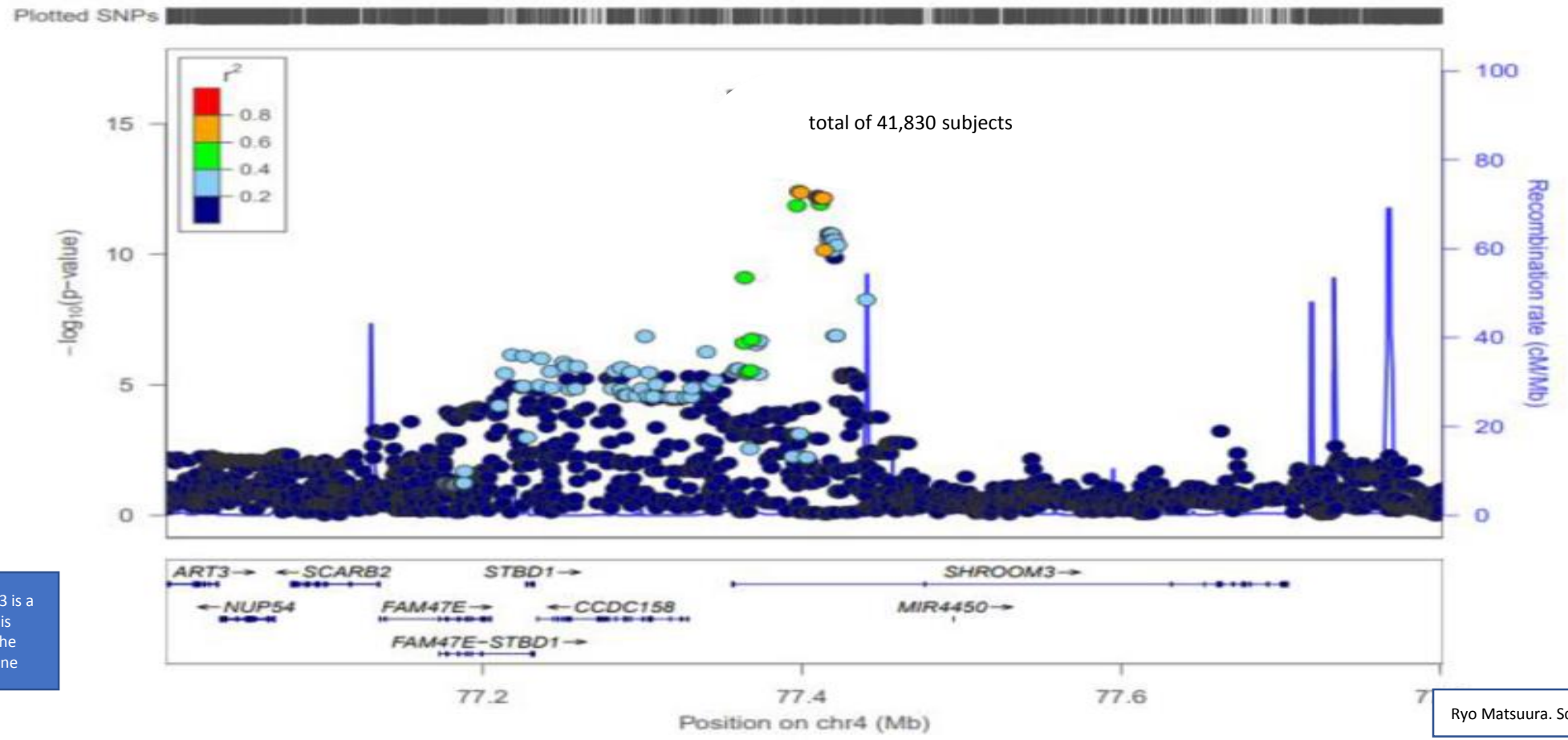


In this GWAS pedigree-based analyses , They also detected a genome-wide significant signal at the UMOD locus (rs28544423, OR = 1.16, 95% CI: 1.10–1.22, P = 1.2 × 10−8), a known GWAS risk locus in Europeans

UMOD is the most abundant protein found in urine and has emerged as a promising biomarker of tubule health

Ning Shang, NPJ, 2021

SHROOM3, the gene associated with CKD in Asians

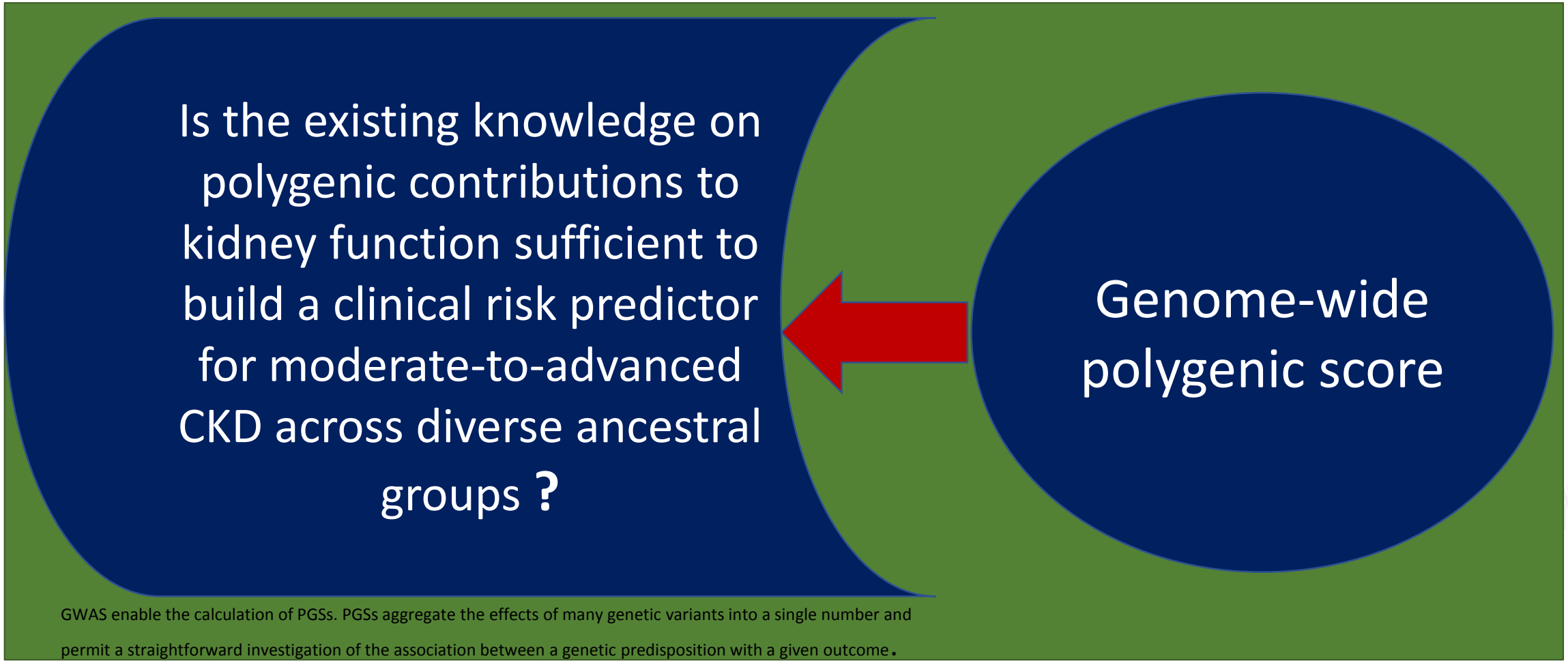


They identified a greater number of tag variants related to shroom family member 3

Protein shroom3 is a protein that is encoded by the SHROOM3 gene

Ryo Matsuura. Scientific reports, 2020

Genome-wide polygenic score to predict CKD



GWAS enable the calculation of PGSs. PGSs aggregate the effects of many genetic variants into a single number and permit a straightforward investigation of the association between a genetic predisposition with a given outcome.

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Genome-wide polygenic score to predict chronic kidney disease across ancestries

Atlas Khan[1], Michael C. Turchin[2], Amit Patki[3], Vinodh Srinivasasainagendra[3], Ning Shang[1], Rajiv Nadukuru[4], Alana C. Jones[5], Edyta Malolepsza[6], Ozan Dikilitas[7], Iftikhar J. Kullo[7], Daniel J. Schaid[7], Elizabeth Karlson[8], Tian Ge[9], James B. Meigs[10], Jordan W. Smoller[9], Christoph Lange[11], David R. Crosslin[12], Gail P. Jarvik[13], Pavan K. Bhatraju[14], Jacklyn N. Hellwege[15], Paulette Chandler[16], Laura Rasmussen Torvik[17], Alex Fedotov[18], Cong Liu[19], Christopher Kachulis[6], Niall Lennon[6], Noura S. Abul-Husn[2,20,21], Judy H. Cho[4], Iuliana Ionita-Laza[22], Ali G. Gharavi[1], Wendy K. Chung[23], George Hripcsak[19], Chunhua Weng[19], Girish Nadkarni[4], Marguerite R. Irvin[5], Hemant K. Tiwari[3], Eimear E. Kenny[2,20,24], Nita A. Limdi[25], Krzysztof Kiryluk[1]

[1]Division of Nephrology, Dept of Medicine, Vagelos College of Physicians & Surgeons, Columbia University, New York, NY

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[4]The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

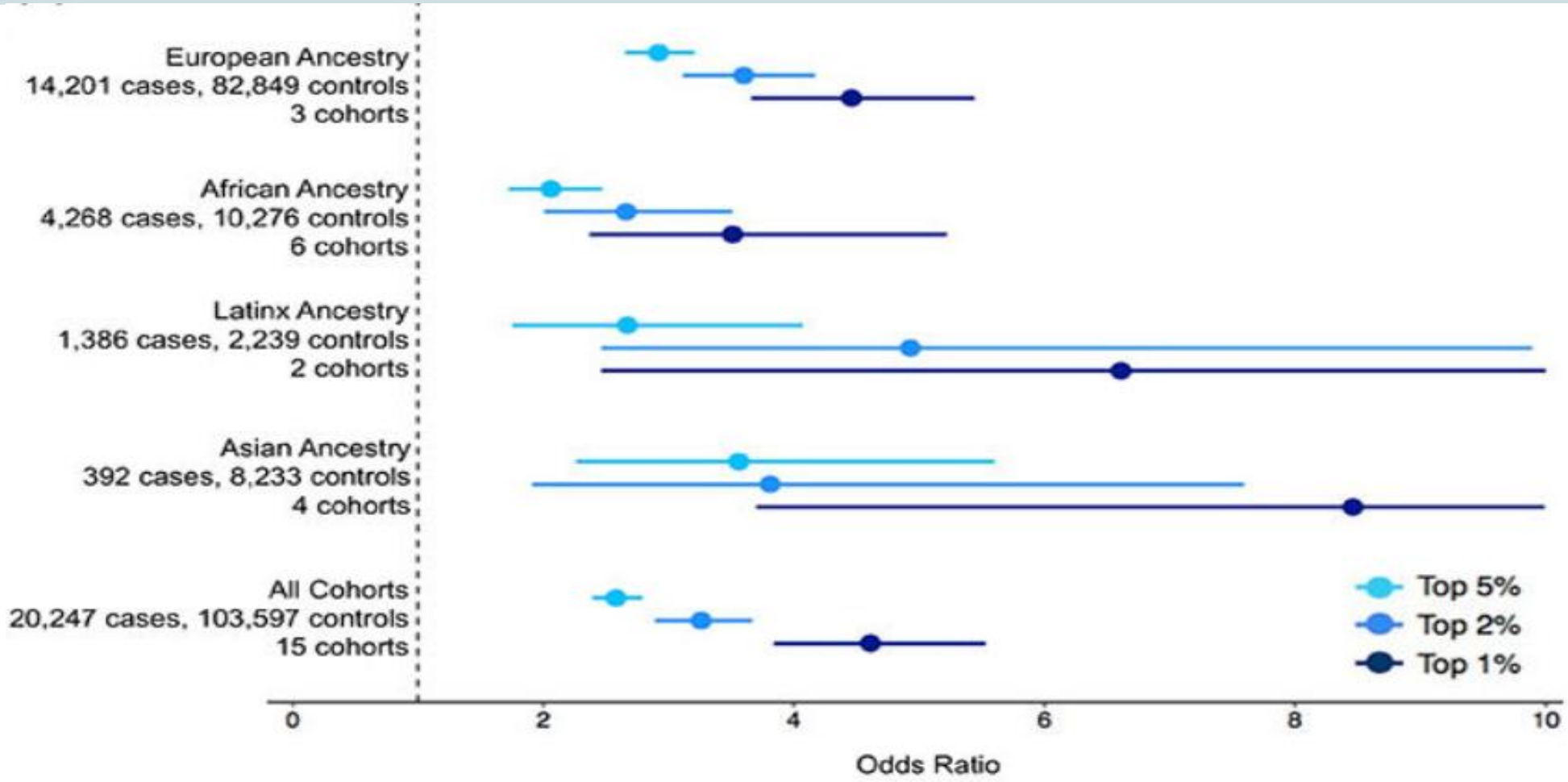
[5]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham,

This study generated and optimized a polygenic score for CKD across 15 cohorts of different ancestries

Genome-wide polygenic score(GPS) across ancestries

GPS in 15 independent and ancestrally diverse case-control cohorts top 2% conveyed approximately 3-fold increase in the disease risk across all ancestries.

The X-axis depicts odds ratio of CKD, the Y-axis depicts testing cohort meta-analysis by ancestry .The effect estimates and 95% confidence intervals) are provided for the top 5%), top 2% top 1%



Atlas Khan. Nat Med, 2023

Conclusion

1- CKD may not represent a single phenotype but rather a collection of genetically and phenotypically heterogeneous diseases encompassing multiple Mendelian subtypes, as well as disorders of more complex genetic determination.

2- GWAS can identify CKD patients with rapid deterioration of kidney function and can identify pre- symptomatic individuals who are at higher risk of progressing to CKD.

thank YOU

Slide 1

CKD has become a serious public health problem because of its associated morbidity, premature mortality, and attendant healthcare costs. The rising number of persons with CKD is linked with the aging population structure and an increased prevalence of diabetes, hypertension, and obesity. CKD can be caused by systemic or primary renal diseases.. The cause of CKD remains unexplained in approximately 20% of patients. Retrospective studies indicate that there are genetic causes in 10%–50% of patients with unexplained CKD.

Slide 2

There is an inherited risk associated with developing CKD, as evidenced by familial clustering and differing prevalence rates across ethnic groups. Approximately, 30% of patients with CKD report a positive family history of kidney disease . In addition, African-Americans, Hispanics, Native Americans, and people of South Asian origin have a higher risk of CKD

Diabetes and hypertension are major risk factors, but do not account for all of the risk. Therefore, in many cases a hereditary origin for the disease should be considered

As you know, CKD frequently worsens in severity over time. but, declines in renal function can vary substantially between individuals despite similar etiologies, optimal BP and BS control. It seems many genetic risk factors can contribute to the CKD progression

,

Skrunes R. Clin J Am Soc Nephrol 2014

Groopman EE. N Engl J Med 2019

✓Slide3

At first I want to explain a little about Heritability of CKD. As you Know, Clinical factors account for less than one half of the observed variability

Heritability measures the fraction of phenotype variability that can be attributed to genetic variation. This study that was done in 2021 , is the largest and most comprehensive pedigree-based analysis of heritability for kidney function, albuminuria, and CKD presently

And strongly supported significant genetic contributions to renal function .Based on 2623 pedigrees with adequate phenotype data, they estimated the overall observational heritability of eGFR at 0.214 (95% CI: 0.142–0.286, $P = 4.3 \times 10^{-5}$) and as you see, and was increased with kidney function deterioration

They also found that heritability was higher for African Americans when compared to other ancestral groups

In addition , observational heritability was increased in higher degrees of albuminuria

✓Slide 3

- ✓In this slide you can see risk factors associated with CKD progression in the CRIC Study
- ✓CRIC Study is an ongoing, multicenter, longitudinal study of more than 5000 adults with CKD. Over the past 10 years, the CRIC Study reported factors associated with CKD progression and found that genetic components contribute to this complex heterogeneous disease

✓Slide 5

This is human nuclear genome. less than 2% of the entire human genome encodes proteins referred to as the exome. Of the human exome , 18 % is associated with monogenic diseases with a mendelian inheritance. From these genes (Mendeliome), about 600 are currently associated with kidney disease.

Exons refer to the coding portions of DNA. And introns refer to non-coding sequences found in DNA Bassanese G. Orphanet J Rare Dis, 2021

High heritability of CKD is attributed to both monogenic and polygenic causes. Monogenic diseases are very important cause of CKD. They account for 10–15% of the prevalence of ESRD in adults. SNP is a genomic variant at a single base position in the DNA.

On the other hand , CKD as a Complex or multifactorial disease have a polygenic inheritance.

, meaning that SNPs in many genes need to be combined to form an effective genetic risk profile. This profile can identify CKD patients who their kidney function were rapidly deteriorated and help to identify pre symptomatic individuals who are at higher risk of progressing to CKD .

Therefore, In addition to genetic causality of renal disease, genetic factors have a role in determining kidney function, the risk of, severity and progression of kidney disease

Monogenic kidney disease is caused by rare pathogenic variants in a single gene . and environmental factors have limited influence

On the other hand , CKD have a polygenic inheritance and depend on the interactions between multiple genetic variants and environmental factors. They lack simple patterns of inheritance (e.g., dominant, recessive, or sex-linked) .

As you see, genetic risk variants for kidney diseases occur on a spectrum from rare variants with large effects to common variants with small effects, and many diseases do not fit neatly into either category and are influenced by the aggregate effect of many common genetic variants in multiple genomic regions, as well as environmental factors.

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When we want to consider the cause of kidney disease , we can approach by MPS techniques (previously referred to as NGS)

There are 3 NGS approaches: targeted panel sequencing, WES, WGS

In TGP, only coding portions of a specific set of genes are targeted but WES captures all coding sequences in the genome, and WGS covers nearly all regions of the genome.

When we want to detect genetic risk factors associated with common, complex diseases such as CKD, we have to do GWASs .

The number of genes that have been implicated in human kidney diseases or variation in kidney function is very large and Many genetic loci have been associated with CKD based on GWAS

Unfortunately, these studies involved predominantly European cohorts. The latest study involved 765,348 participants. but more than 70% of which were European

Anyway ,The APOL1 , uromodulin , AGT and RENBP genes were strongly associated with CKD progression .

Recently , association of Shroom 3 gene with kidney function in the Asian population has been reported.

- ✓ Genetic variants in APOL1 are relatively common among individuals of African ancestry. Approximately 13% of Africans carry two APOL1 risk alleles .these alleles are a frequent cause of kidney disease

. they evaluated 2955 white patients and black patients with CKD(46% of whom had diabetes) according to whether they had 2 copies of high-risk APOL1 variants (APOL1 high-risk group) or 0 or 1 copy (APOL1 low-risk group)

The primary outcome was defined as a doubling of the serumcreatinine level from baseline or incident ESRD

- ✓ given that earlier analyses were conducted in Western populations, it remains unknown which genetic loci are associated with kidney function in the Asians population. This GWAS using the Biobank Japan dataset by excluding secondary kidney diseases, examined the effects of common genetic variants on CKD progression. Although, GWAS identified several genetic loci associated with indices of kidney function , However, most of these studies included D.M in their analyses, but this study exclude diabetes to find more primary genetic factors responsible for kidney function decline
- ✓ They showed that half of the top 50 SNPs associated with eGFR are located in the SHROOM3 gene, suggesting that SHROOM3 will be responsible for kidney function , with rs142647267 shown to be the most significant

Genome-wide polygenic score to predict CKD across ancestries

- ✓ this study developed a GPS for CKD that predicts CKD across four ancestry groups
- ✓ By combining APOL1 risk genotypes with GWAS for kidney function, this study designed a GPS for CKD that was tested in 15 independent cohorts, including
- ✓ 3 cohorts of European ancestry (total N=97,050), 6 cohorts of African ancestry (total N=14,544),
- ✓ 4 cohorts of Asian ancestry (total N=8,625), and 2 admixed Latinx cohorts (total N=3,625).
- ✓ This study revealed significant associations between a polygenic predisposition to lower eGFR , KF, and death among persons with moderate CKD, emphasizing the importance of genetic background even after disease onset.
- ✓

- ✓ The CRIC Study is a multicenter, prospective study of racially and ethnically diverse patients with CKD. Although the original aims of the study were to identify novel predictors of CKD progression among nearly 4000 individuals with CKD, the CRIC Study has evolved into a national resource for investigation of a broad spectrum of CKD-related topics. The study enrolled adults aged 21 to 74 years with a broad spectrum of renal disease severity
- ✓ The primary renal outcome measure was reduction in estimated GFR. Renal events were defined as the need for RRT, an estimated halving of GFR, and/or a 25 ml/min per 1.73 m2 decline in GFR from baseline
- ✓ The study enrolled participants with CKD aged 21 to 74 years.
- ✓ The cohort is racially and ethnically diverse with 1638 (45%) non-Hispanic white patients, 1651 (46%) non-Hispanic black/African American patients, 169 (5%) Hispanic patients, and 154 (4%) Asian/Pacific Islander/Native American patients.
- ✓ strongly support the hypothesis that the presence of high-risk variants of APOL1 accelerates CKD progression in blacks with CKD, regardless of the cause of the underlying kidney disease