



University  
of Dundee

# GWAS analysis of type 2 diabetes with and without Diabetic Kidney Disease (DKD) in South Indians

By

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# Outline...

Work Progress

Background

Definition and Characterization of Diabetes Kidney Disease

Study Design

Clinical Parameters for the study

Workflow

# Work done so far...

DNA Extraction >2500 Samples

GWAS >25 Batches

## Fundamentals of Bioinformatics

Linux/Ubuntu Platforms

## Bioinformatics tools:

❖ PLINK

❖ R

The screenshot displays a Linux desktop environment. On the left is a vertical dock with application icons. The main workspace contains a terminal window and a file manager window. The terminal window shows the following R code and output:

```
illuminaiscan@illuminaiscan-B250M-D2V: ~/t16 1
b> Type 'contributors()' for more information and
en 'citation()' on how to cite R or R packages in publications.

Type 'demo()' for some demos, 'help()' for on-line help, or
'help.start()' for an HTML browser interface to help.
Type 'q()' to quit R.

6.0
is.
> freq=read.table("casecon.qc.ind.freq.frq", header=T)
Error in file(file, "rt") : cannot open the connection
In addition: Warning message:
In file(file, "rt") :
cannot open file 'casecon.qc.ind.freq.frq': No such file or directory
il
> freq=read.table("b16.qc.ind.freq.frq", header=T)
> png("casecon_qcind_freq.png", res=1200, width=4, height=4,
+
> png("b16_qcind_freq.png", res=1200, width=4, height=4, units="in")
> par(mfrow=c(1,1))
> hist(freq$MAF, ylab="Number of SNPs", xlab="MAF", main="Minor
+ allele frequencies")
une
> abline(v=0.01, lty=2) #1% MAF
c.p
onull device
1
>
```

The file manager window shows a histogram titled "Minor allele frequencies". The y-axis is labeled "Number of SNPs" and ranges from 0 to 200,000. The x-axis is labeled "MAF" and ranges from 0.0 to 0.5. The histogram shows a high frequency of SNPs with low MAF, with a vertical dashed line at MAF = 0.01. The file name "b16\_qcind\_freq.png" is visible in the window title bar.

At the bottom right of the terminal window, a status bar indicates: "b16\_qcind\_freq.png" selected (135.8 kB)

# Background

- Chronic Kidney Disease is "progressive," which means it gets worse over time. An estimated 750 million people have **chronic kidney disease** globally . ( **Bello *et al*** )
- **Diabetic Kidney Disease** (earlier called **Diabetic nephropathy**) results when diabetes damages the blood vessels and other cells in kidney . Over time uncontrolled diabetes can cause damage to blood vessels in the kidney.
- Kidney disease in diabetic patients is clinically characterized by increasing rates of urinary albumin excretion, starting from normalalbuminuria, which progresses to microalbuminuria, macroalbuminuria, and eventually to **end-stage renal disease** (ESRD).
- Studies conducted in migrant Asian Indians in the U.K. and European have reported increased prevalence of diabetic nephropathy compared with white Caucasians. Diabetic kidney disease is the leading cause of an ESRD worldwide, and it is estimated that 20% of type 2 diabetic patients reach ESRD during their lifetime. ( **R Unnikrishnan *et al* 2007** )

# Definition and characterization of Diabetic Kidney Disease

**Diabetic Kidney disease** is defined as:

- ❑ Albuminuria (albumin-to-creatinine ratio  $\geq 3.4$  mg/mmol [30 mg/g])
- ❑ Estimated glomerular filtration rate (eGFR)  $< 60$  ml/min/1.73m<sup>2</sup>.
- ❑ Diabetes is defined as fasting glucose  $\geq 7$  mmol/L (126 mg/dL) and/or use of medications for diabetes;
- ❑ Hypertension as systolic BP  $\geq 140$ mmHg and diastolic  $\geq 90$ mmHg and/or use of medications for hypertension. (**Anand et al CAARS STUDY 2017**)

**There are no data on the GWAS of diabetic kidney disease in Indians.**

# Broad objectives of my Study

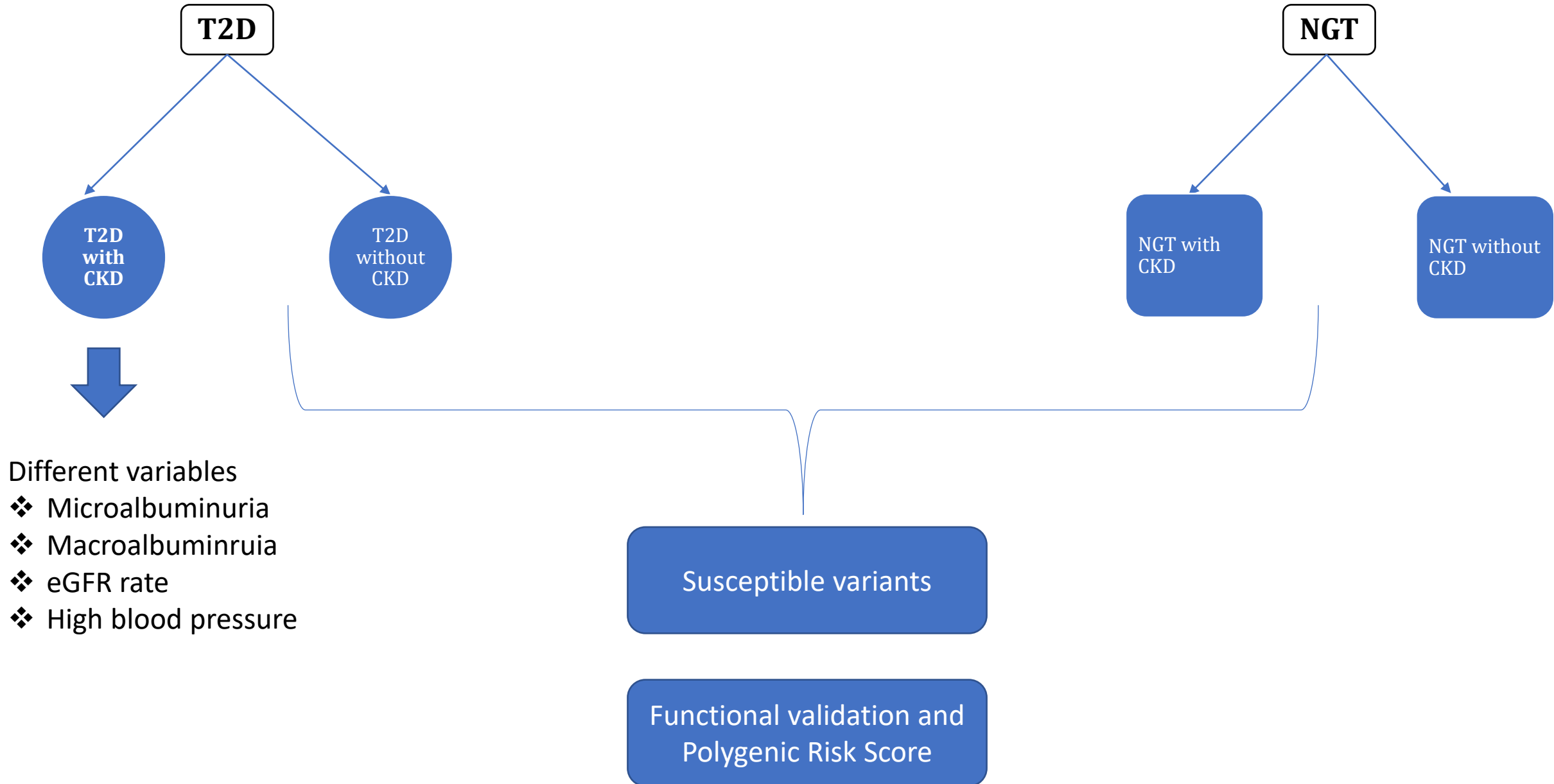
1. To identify the genetic markers associated with Diabetic Kidney Disease in South Indian population using Genome-wide association studies.
2. To carry out functional validation for the rare variants from GWAS Analysis.
3. To construct a Polygenic Risk Score (PRS) for DKD in South Indian population.

# CLINICAL VARIABLES that will be considered for the study

- Age
- Gender
- Waist measurement
- BMI
- Blood pressure
- Lipid levels
- Retinopathy /Cardio vascular disease
- HbA1c
- Microalbuminuria ( 30 – 299 mg/mmol )
- Macro albuminuria ( >300 mg/mmol )
- eGFR rate



# GWAS Analysis-Work flow



## References

- Unnikrishnan R, Rema M, Pradeepa R, Deepa M, Shanthirani CS, Deepa R, Mohan V. Prevalence and risk factors of diabetic nephropathy in an urban South Indian population: the Chennai Urban Rural Epidemiology Study (CURES 45). *Diabetes Care*. 2007 Aug;30(8):2019-24. doi: 10.2337/dc06-2554. Epub 2007 May 8. PMID: 17488949.
- Anand S, Kondal D, Montez-Rath M, Zheng Y, Shivashankar R, Singh K, Gupta P, Gupta R, Ajay VS, Mohan V, Pradeepa R, Tandon N, Ali MK, Narayan KM, Chertow GM, Kandula N, Prabhakaran D, Kanaya AM. Prevalence of chronic kidney disease and risk factors for its progression: A cross-sectional comparison of Indians living in Indian versus U.S. cities. *PLoS One*. 2017 Mar 15;12(3):e0173554. doi: 10.1371/journal.pone.0173554. PMID: 28296920; PMCID: PMC5351850.
- Guan M, Keaton JM, Dimitrov L, Hicks PJ, Xu J, Palmer ND, Ma L, Das SK, Chen YI, Coresh J, Fornage M, Franceschini N, Kramer H, Langefeld CD, Mychaleckyj JC, Parekh RS, Post WS, Rasmussen-Torvik LJ, Rich SS, Rotter JI, Sedor JR, Thornley-Brown D, Tin A, Wilson JG, Freedman BI, Bowden DW, Ng MCY; FIND Consortium. Genome-wide association study identifies novel loci for type 2 diabetes-attributed end-stage kidney disease in African Americans. *Hum Genomics*. 2019 May 15;13(1):21. doi: 10.1186/s40246-019-0205-7. PMID: 31092297; PMCID: PMC6521376.
- Spray BJ, Atassi NG, Tuttle AB, et al. Familial risk, age at onset, and cause of end-stage renal disease in white Americans. *J Am Soc Nephrol*. 1995;5: 1806–10

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THANK YOU