Phenotypic and genotypic determinants of glycaemic deterioration rate in South Indian Type 2 diabetes population

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OUTLINE

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2. Objectives
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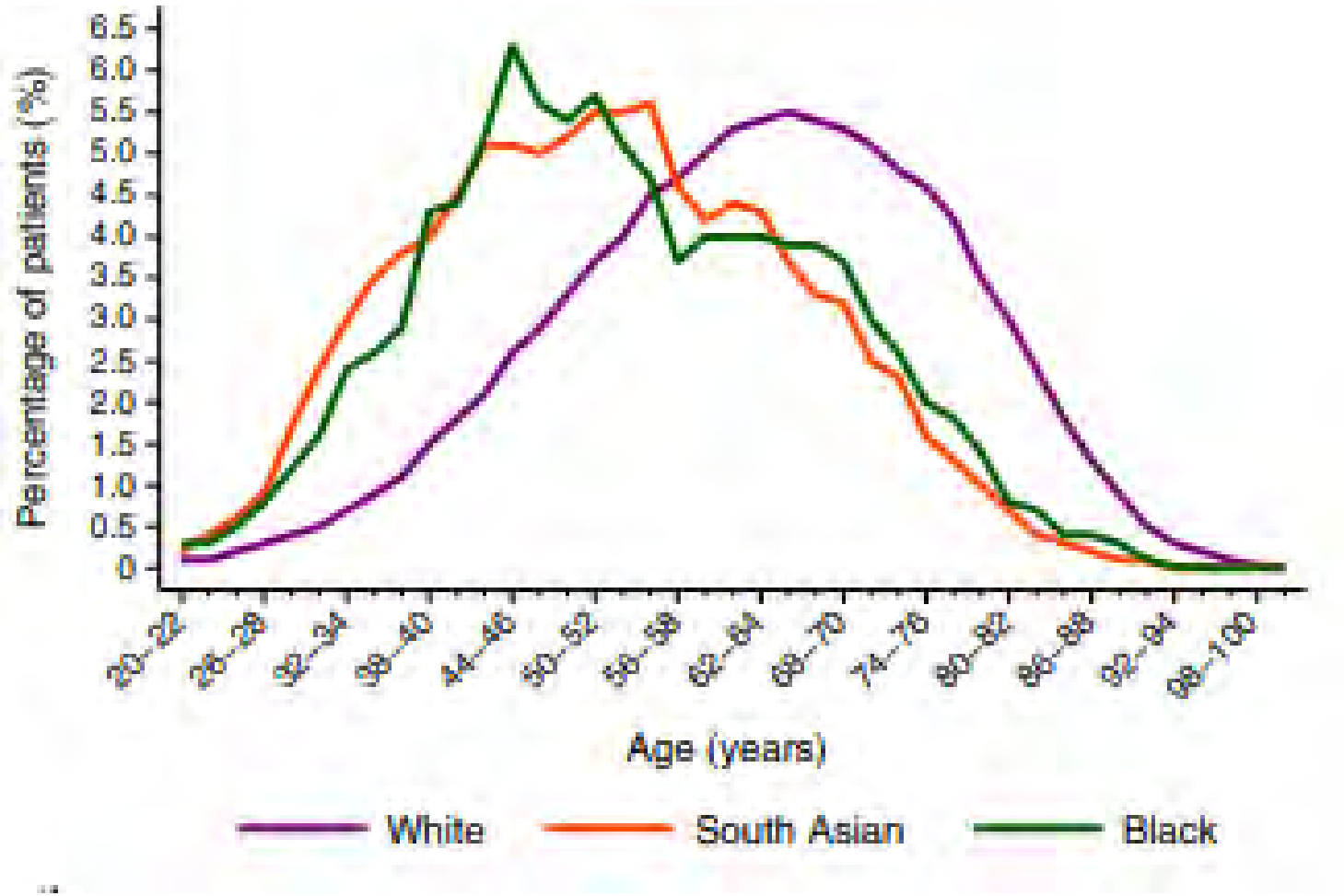
5. Summary

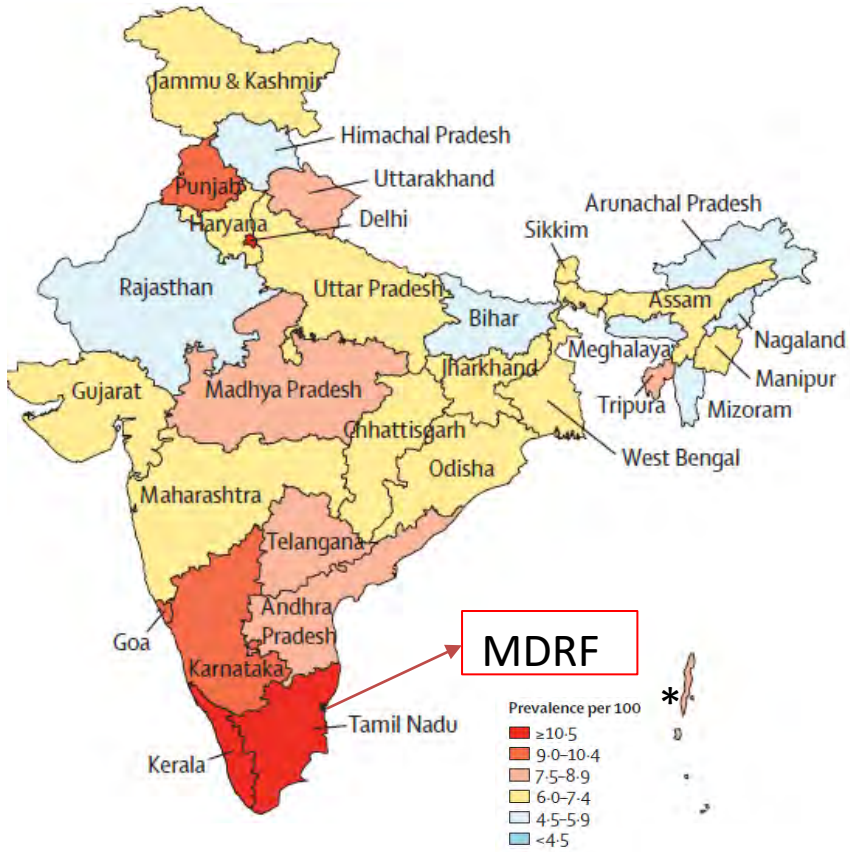
INTRODUCTION

BACKGROUND

- T2D is a heterogenous progressive disease condition with cases having unique disease progression pathways.[1]
- Identifying faster progressors will help in provision of personalized intensive diabetes management to delay the progression
- Age of diagnosis, baseline HDL-c, HbA1c, BMI are major factors associated with T2D progression.[2,3,4]
- ‘Time to insulin’ models have affected by clinical practice and doctor:patient:socio-cultural factors.
- Glycaemic deterioration or coefficient failure- reports annual rate of glycemic deterioration.
- Most of the studies conducted in European T2D population.

Diabetes Indian perspective





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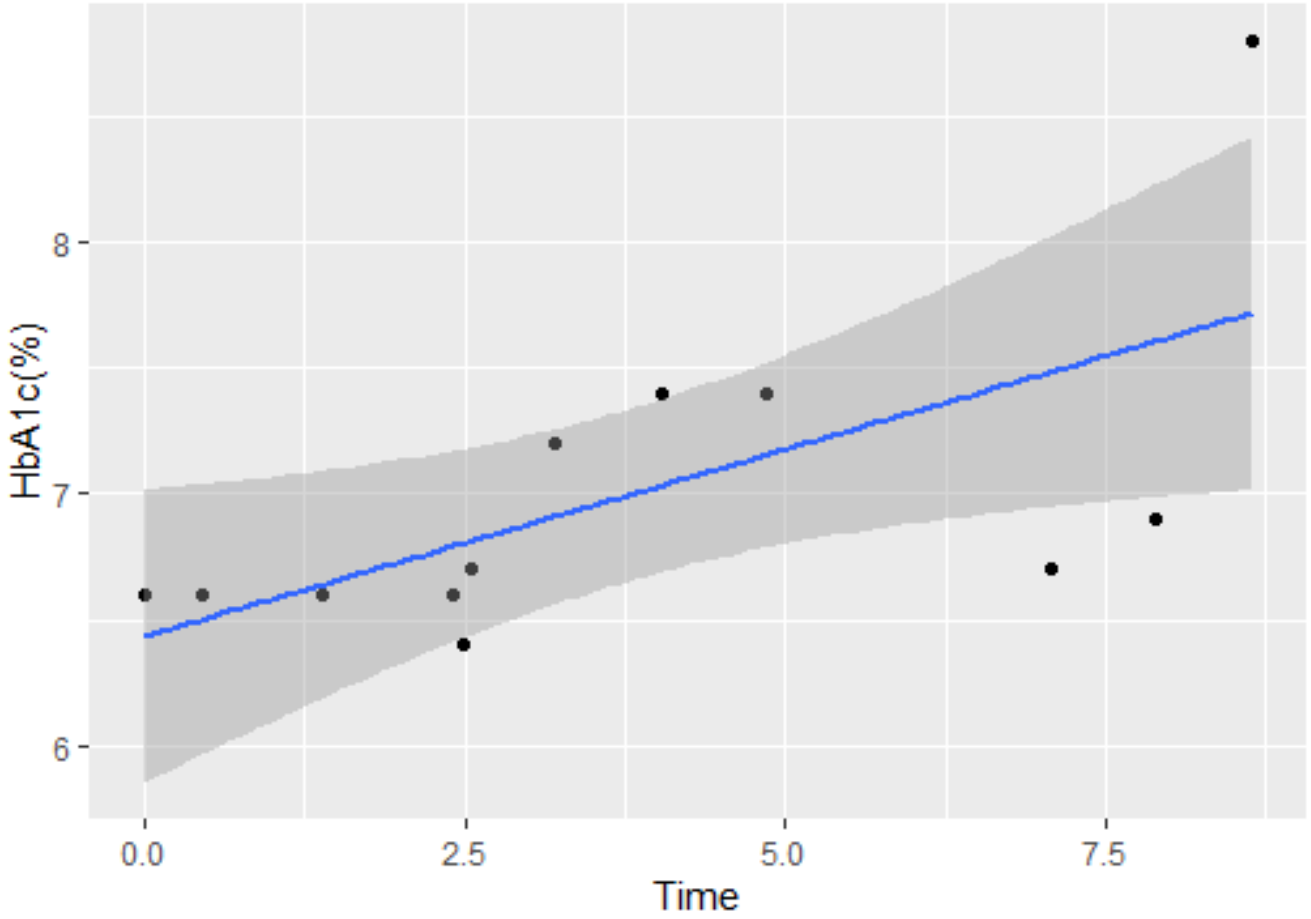
Tandon N, Anjana RM, Mohan V, Kaur T, Afshin A, Ong K, et al. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990–2016. The Lancet Global Health. 2018 Dec 1;6(12):e1352–62

Coefficient of failure/ glycaemic deterioration rate

- Rate of glycaemic deterioration – slope of regression line.
- Previous studies reported Age of diagnosis, HDL-c, beta cell function are associated with rate of glycemic deterioration.[8,9,10]



OBJECTIVES

OBJECTIVES

1. Estimate the ‘coefficient of failure’ in the study population
2. Identify the clinical and lifestyle factors associated with coefficient of failure/glycaemic deterioration in the study population.
3. Identify genetic variants associated with coefficient of failure/glycaemic deterioration.

METHODOLOGY

Data source

- Data source: Madras Diabetes Research Foundation (MDRF)
- Electronic health records generated for each individual and updated in each follow up visit.
- Anonymized data available for epidemiological analysis.
- Data access through secure virtual desktop systems equipped with statistical packages.

Variables used in analysis

- Longitudinal HbA1c,BMI and prescription data
- Variables included in the analysis
  1. Age of diagnosis
  2. Sex
  3. Smoking
  4. Alcohol
  5. Family H/O T2D
  6. Calendar year
  7. BMI
  8. HbA1c
  9. Total Cholesterol
  10. HDL
  11. Triglycerides
  12. HOMA B
  13. HOMA IR

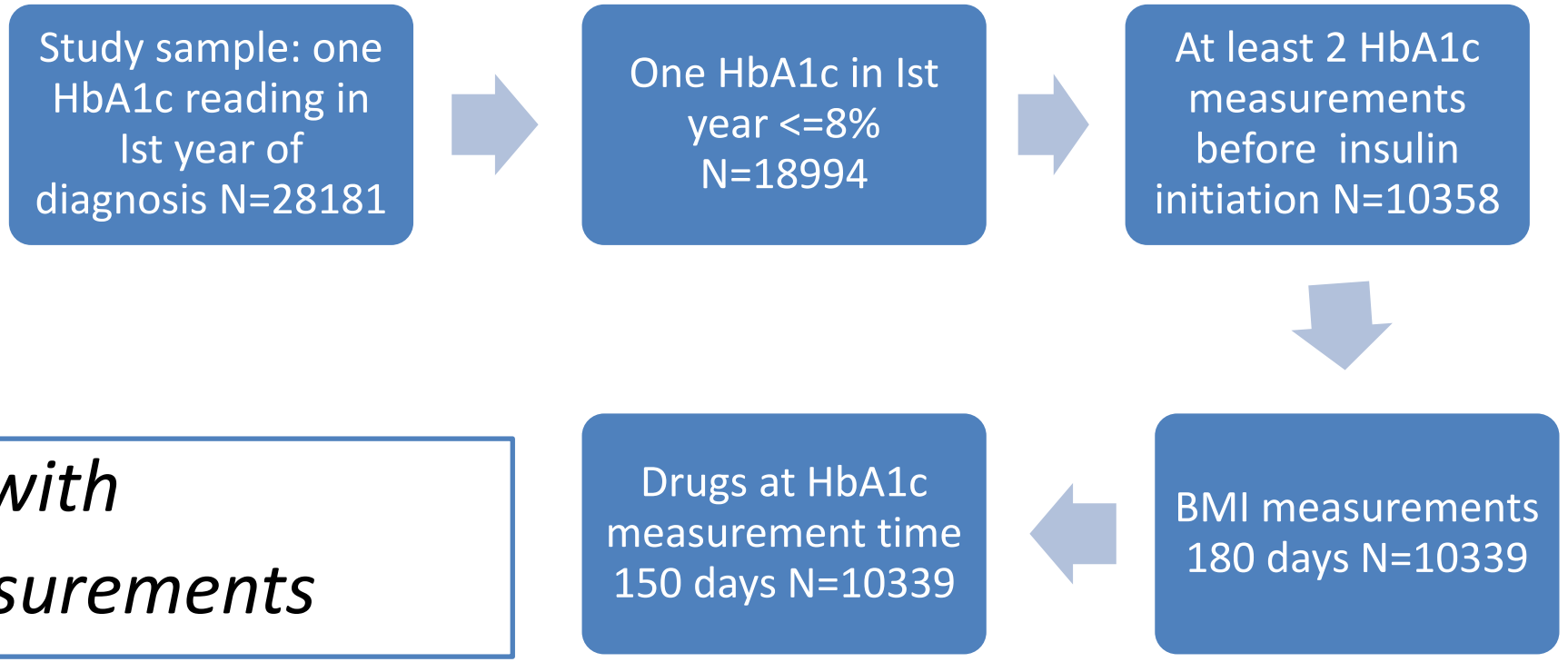
All phenotype recorded within 365 days from date of diagnosis

Analysis description

- Linear Mixed model
  - Fixed and random effects: intercept and slope
  - Longitudinal HbA1c as dependent variable and Change in BMI, drug effect as fixed effect in model, T2D case unique id as random effect.
- Simple linear regression model
  - Glycaemic deterioration rate obtained from linear mixed model as dependent variable and phenotypes and lifestyle factors at diagnosis as independent variable
- Genome wide association studies (GWAS)
  - To detect the variants associated with glycaemic deterioration

RESULTS

Data flow for linear mixed model



10339 individuals with

65803 HbA1c measurements

Mixed model results

Variable	Estimates
BMI stable	Reference
BMI Increase	0.19 (0.17-0.21)
BMI reduction	-0.34 (-0.31- -0.36)

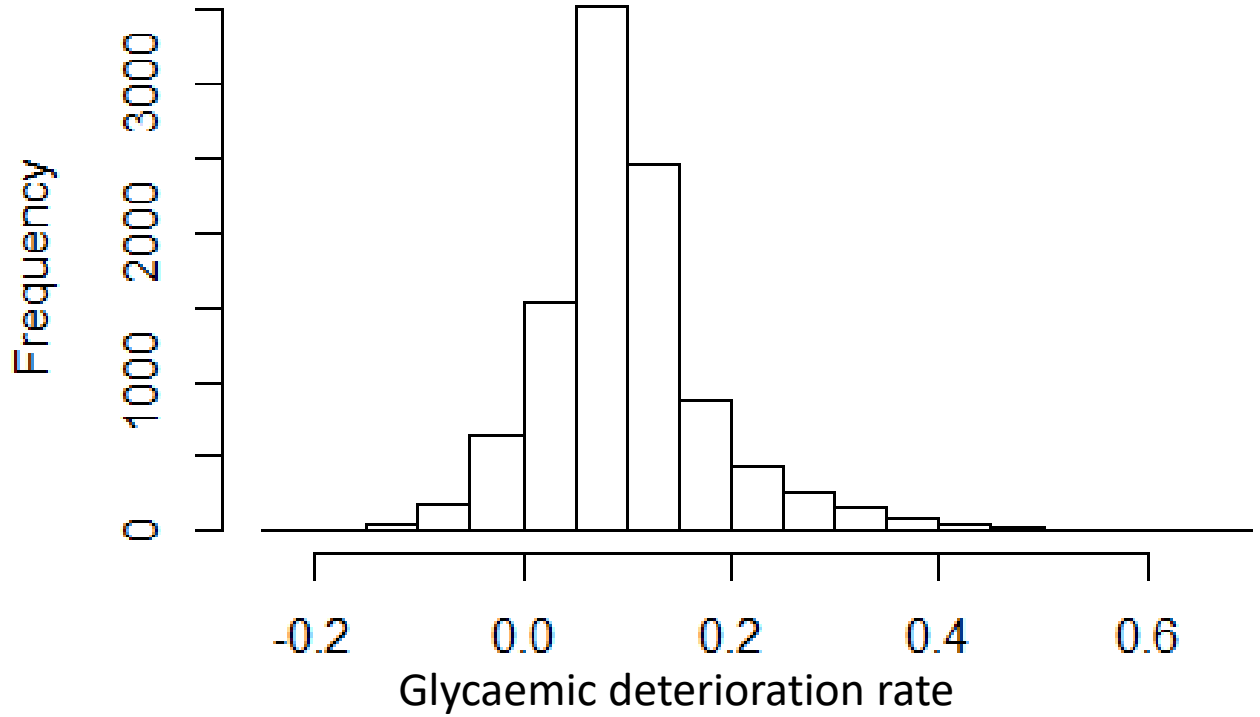
BMI change 5% from baseline

Drug	Estimate (95% CI)
Untreated	Reference
Met	-0.05 (-0.03- -0.07)
AGI	-0.17 (-0.09- -0.24)
DPP	-0.02 (-0.09-0.05)
GLP	-0.13(-0.38- 0.12)
TZD	-0.07 (-0.18- 0.04)
SU	0.00 (-0.02- 0.02)
SGLT	0.10 (-0.15- 0.35)

Glycemic deterioration rate

Mean annual glycemic deterioration	0.098%(95% CI 0.096-0.099)
Median annual glycemic deterioration	0.091% (IQR 0.051-0.125)

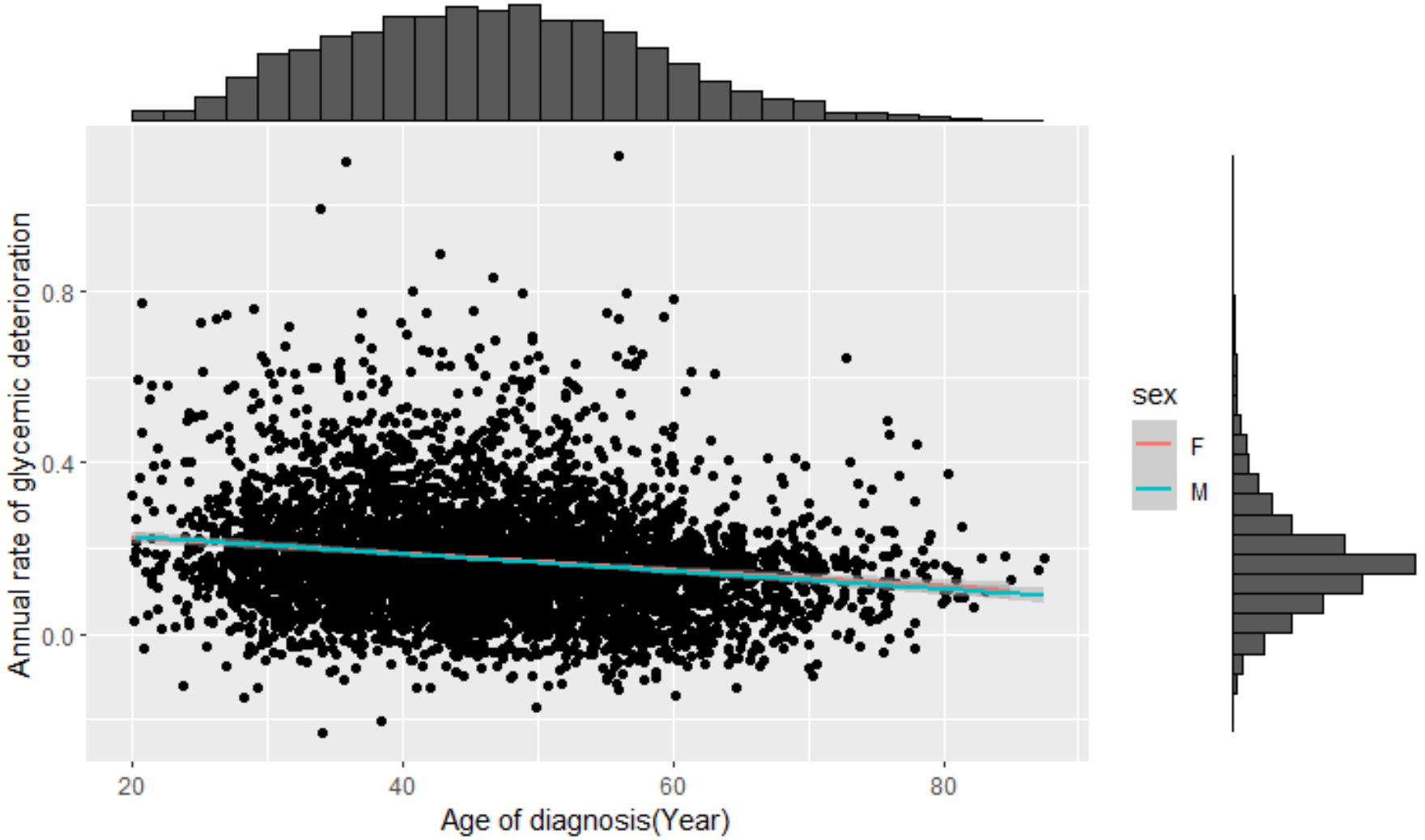
obs.	mean	median	s.d.	min.	max.
10339	0.098	0.091	0.086	-0.221	0.689



Baseline characteristics of the study participants (N=9713)

Variable	Level	Mean(SD)/N(%)
Sex	F	3817 (39.3)
	M	5896 (60.7)
Age of diagnosis	mean (sd)	46.6 (11.5)
HbA1c (%)	mean (sd)	8.9 (2.4)
BMI (kg/m^2)	mean (sd)	27.5 (7.3)
HDL-c (mg/dl)	mean (sd)	39.5 (8.8)
Triglyceride (mg/dl)	mean (sd)	172.2 (134.0)
Total cholesterol (mg/dl)	mean (sd)	184.6 (45.2)
HOMA_IR	mean (sd)	3.3 (13.9)
HOMA_B	mean (sd)	82.0 (59.5)
Family History DM	No H/o DM	4147 (42.7)
	H/o DM	5566 (57.3)
Smoking status	No	7993 (82.3)
	Yes	1720 (17.7)
Alcohol status	No	7469 (76.9)
	Yes	2244 (23.1)

Glycemic deterioration Vs age of diagnosis



Univariate associations
Linear regression

- *Slope from linear mixed model (glycemic deterioration rate) as dependent variable.*
- *A positive estimate indicate it increases rate of glycemic deterioration*
- *A negative estimate denote it decreases rate of glycemic deterioration*

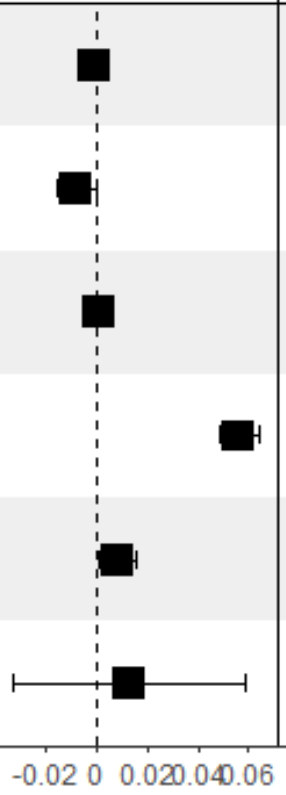
Variable	Level	Estimate
Sex	F	REF
	M	0.01[0.00-0.01]
Age of diagnosis		-0.01[-0.01-0.00]
HbA1c (%)		0.01[0.01-0.01]
BMI (kg/m^2)		0.00[0.00-0.00]
HDL-c (mg/dl)		-0.04[-0.05- -0.02]#
Triglyceride (mg/dl)		0.02[0.01-0.02]#
Total cholesterol (mg/dl)		0.03[0.03-0.05]#
HOMA_IR		0.02[0.01-0.03]#
HOMA_B		-0.02[-0.03- -0.02]#
Family History DM	No H/o DM	REF
	H/o DM	0.01[0.01-0.02]
Smoking status	No	REF
	Yes	0.02[0.01- 0.03]
Alcohol status	No	REF
	Yes	0.01[0.01- 0.02]
Calendar year of diagnosis		0.00[0.00-0.00]

#- log transformed

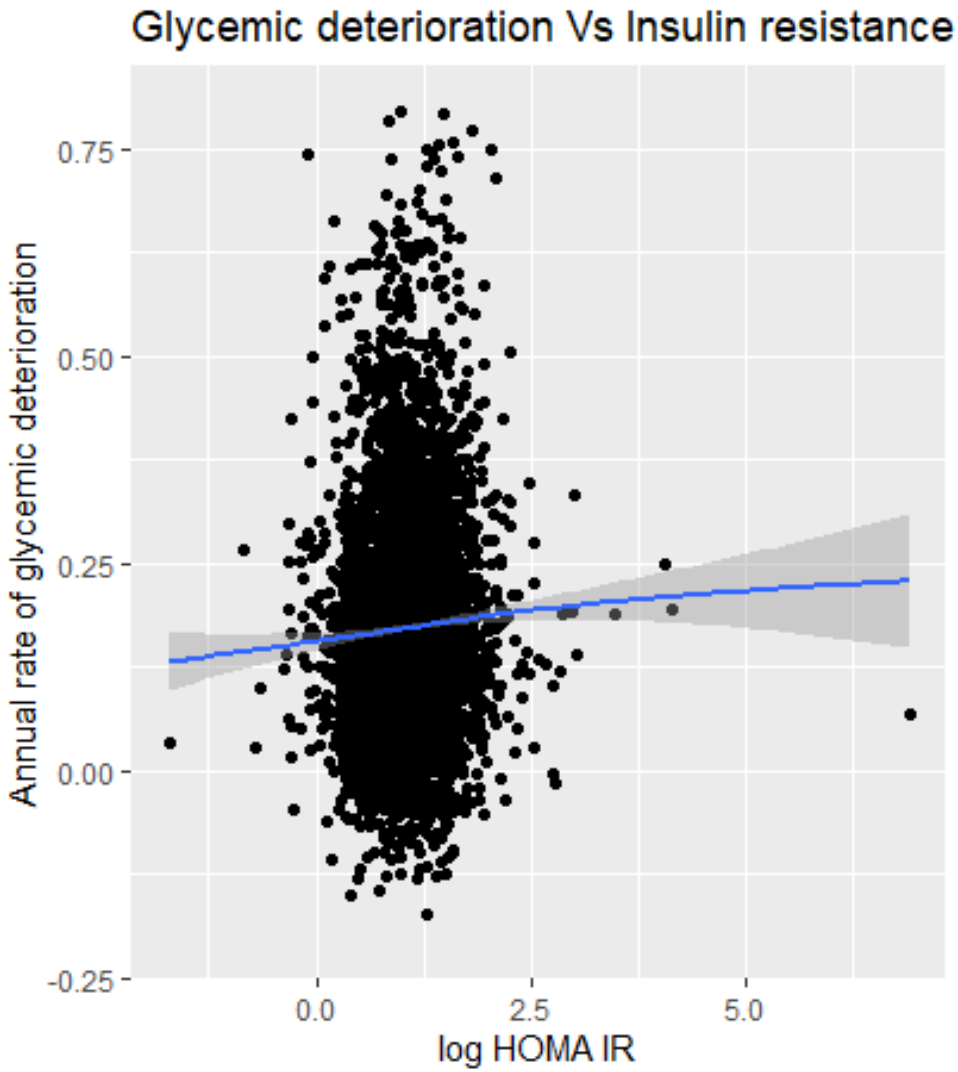
Linear regression analysis

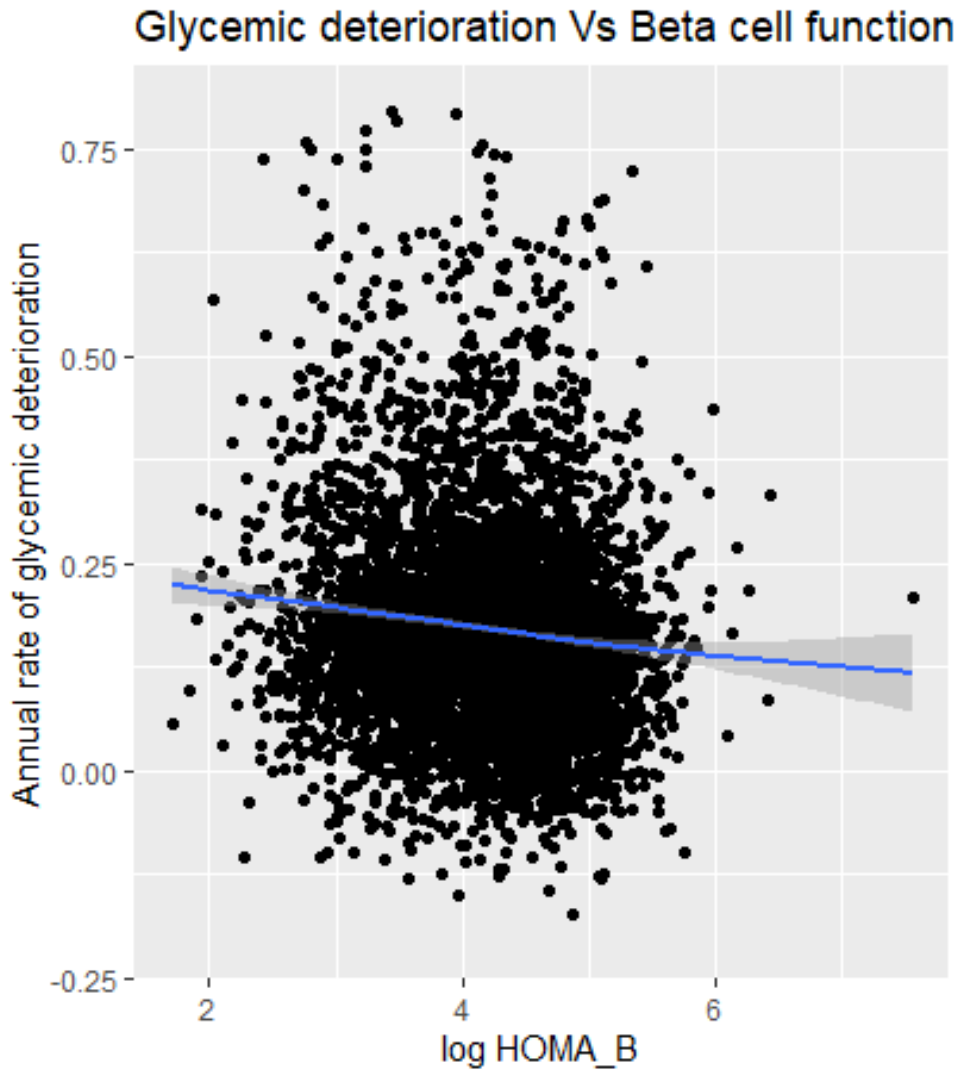
- *Slope from linear mixed model (glycemic deterioration rate) as dependent variable.*
- *A positive estimate indicate it increases rate of glycemic deterioration*
- *A negative value denote it decreases rate of glycemic deterioration*
- *Higher age of diagnosis and elevated HDL-c decreases rate of progression*
- *Higher baseline HbA1c, BMI, dyslipidemia increases rate of progression*

Variable	N	Estimate	p
age_diag	9713	-0.00 (-0.00, -0.00)	<0.001
log(hdl)	9713	-0.01 (-0.02, -0.00)	0.05
BMI_num	9713	0.00 (0.00, 0.00)	0.01
log(hba1c)	9713	0.06 (0.05, 0.06)	<0.001
log(cho)	9713	0.01 (0.00, 0.02)	0.03
(Intercept)		0.01 (-0.03, 0.06)	0.58



Insulin resistance and beta cell function at T2D diagnosis

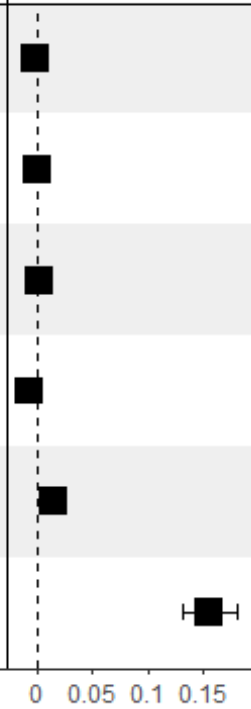




Effect of HOMA B and HOMA IR

- *Slope from linear mixed model (glycemic deterioration rate) as dependent variable.(HOMA B and HOMA IR adjusted for age and sex)*
- *A positive estimate indicate it increases rate of glycemic deterioration*
- *A negative value denote it decreases rate of glycemic deterioration*
- *Higher beta cell function at T2D diagnosis slows the rate of progression*
- *Higher insulin resistance increases rate of progression*

Variable		N	Estimate	p
age_diag		3330	-0.00 (-0.00, -0.00)	<0.001
sex	F	1356	Reference	
	M	1974	0.00 (-0.00, 0.01)	0.477
log(HOMA_B)		3330	-0.01 (-0.01, -0.00)	0.006
log(HOMA_IR)		3330	0.01 (0.01, 0.02)	<0.001
(Intercept)			0.16 (0.13, 0.18)	<0.001



Genetic variants associated with glycemic deterioration rate

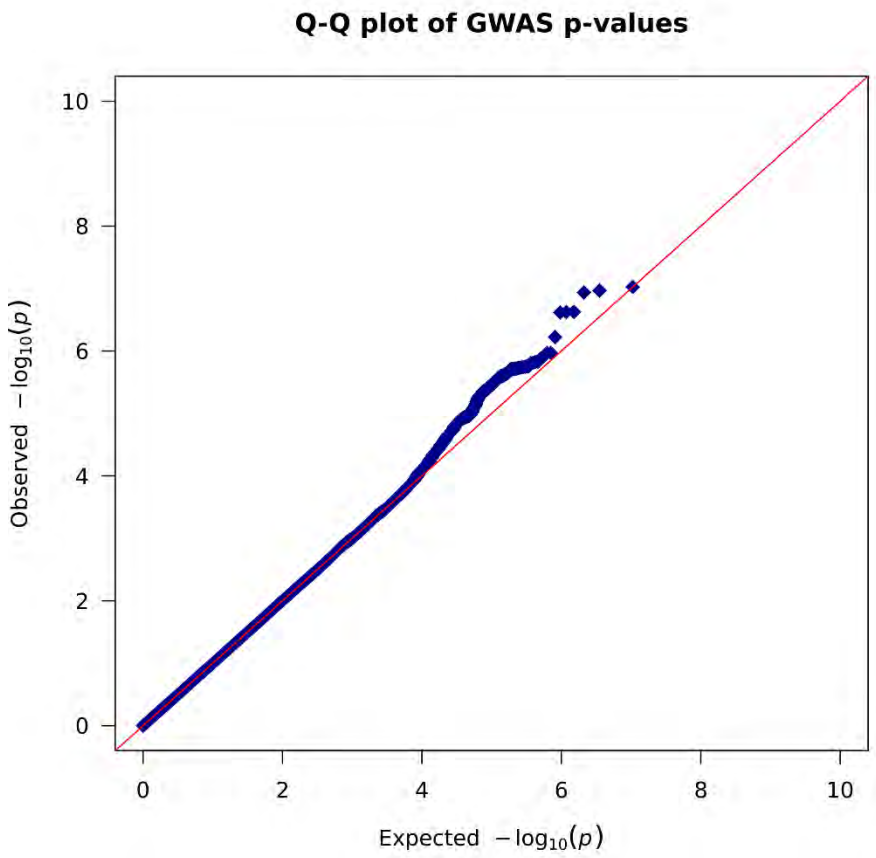
MDRF Freeze 1 (N=718)

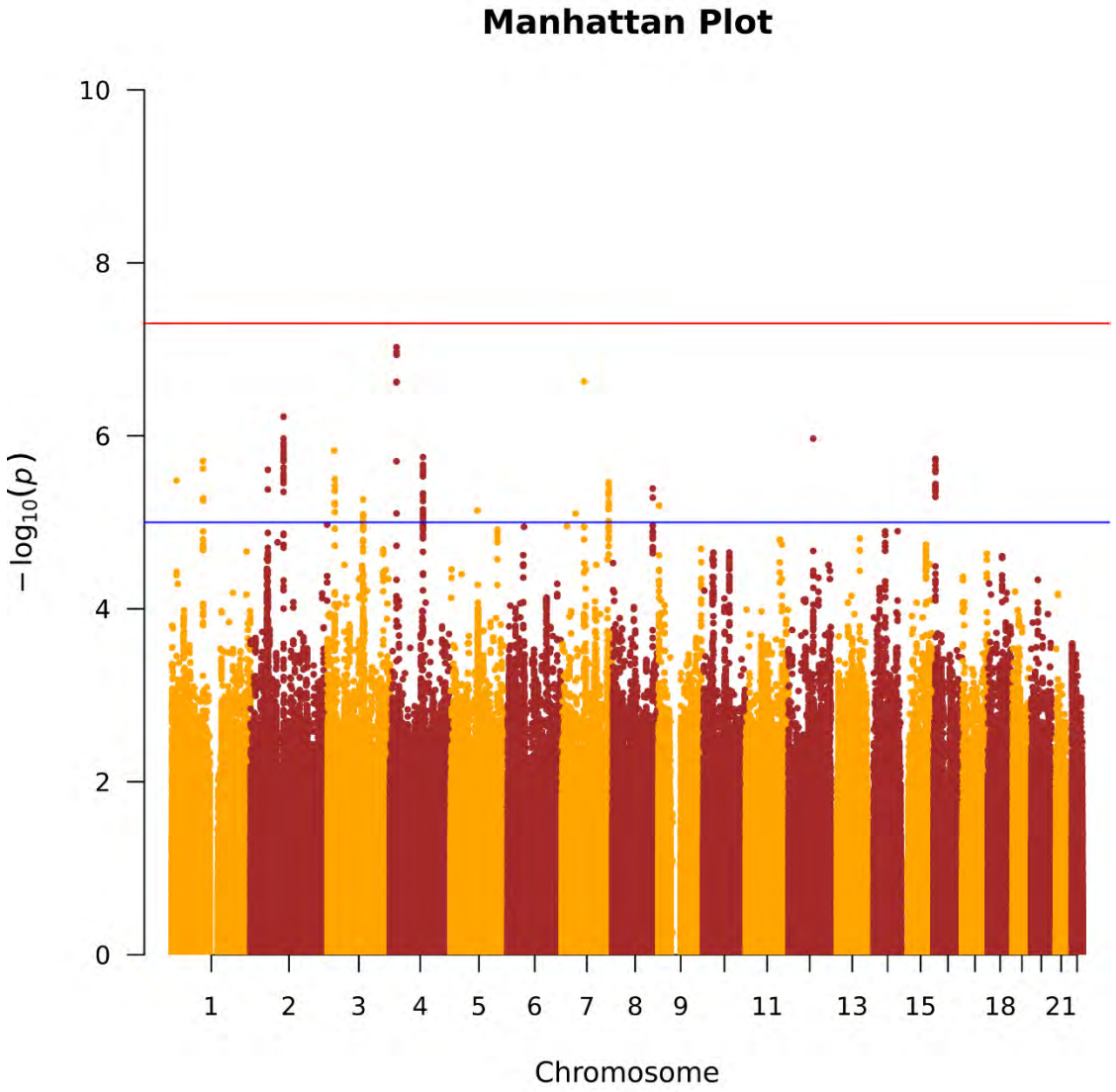
MDRF Freeze 2 (N=292)

- Genome wide association test with glycemic deterioration rate as linear trait
- Age and Sex adjusted model
- Population stratification adjusted with – Principal Components
- MAF >0.05

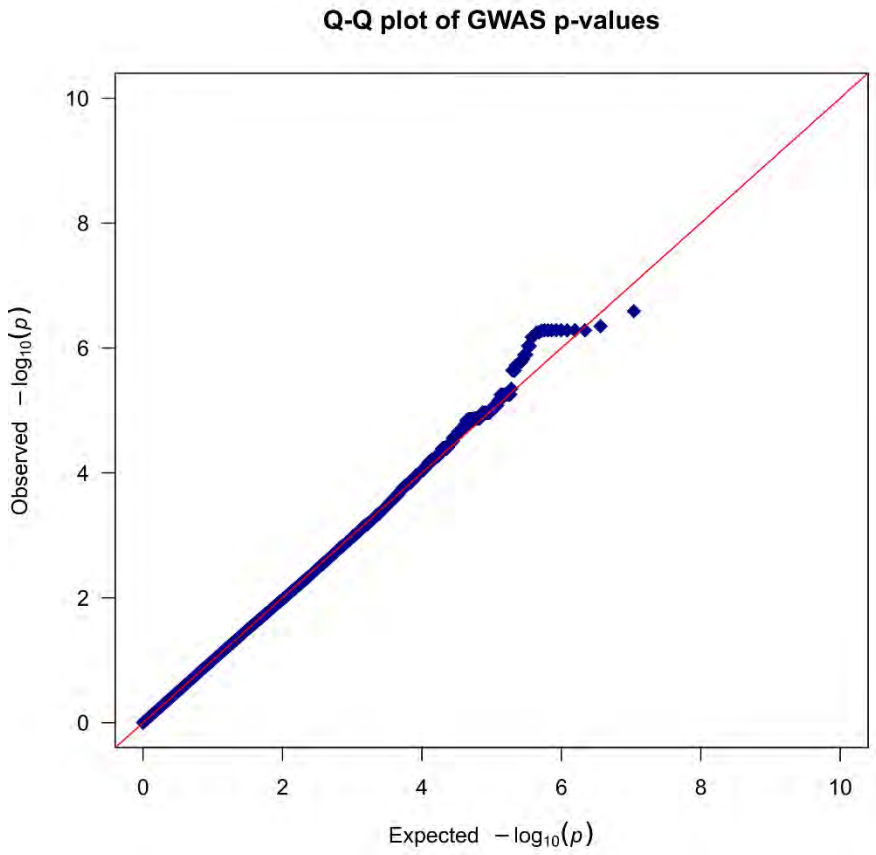
- Combined the results using meta analysis
- Fixed effect meta analysis
- Number of individuals in combined analysis (n=1010)

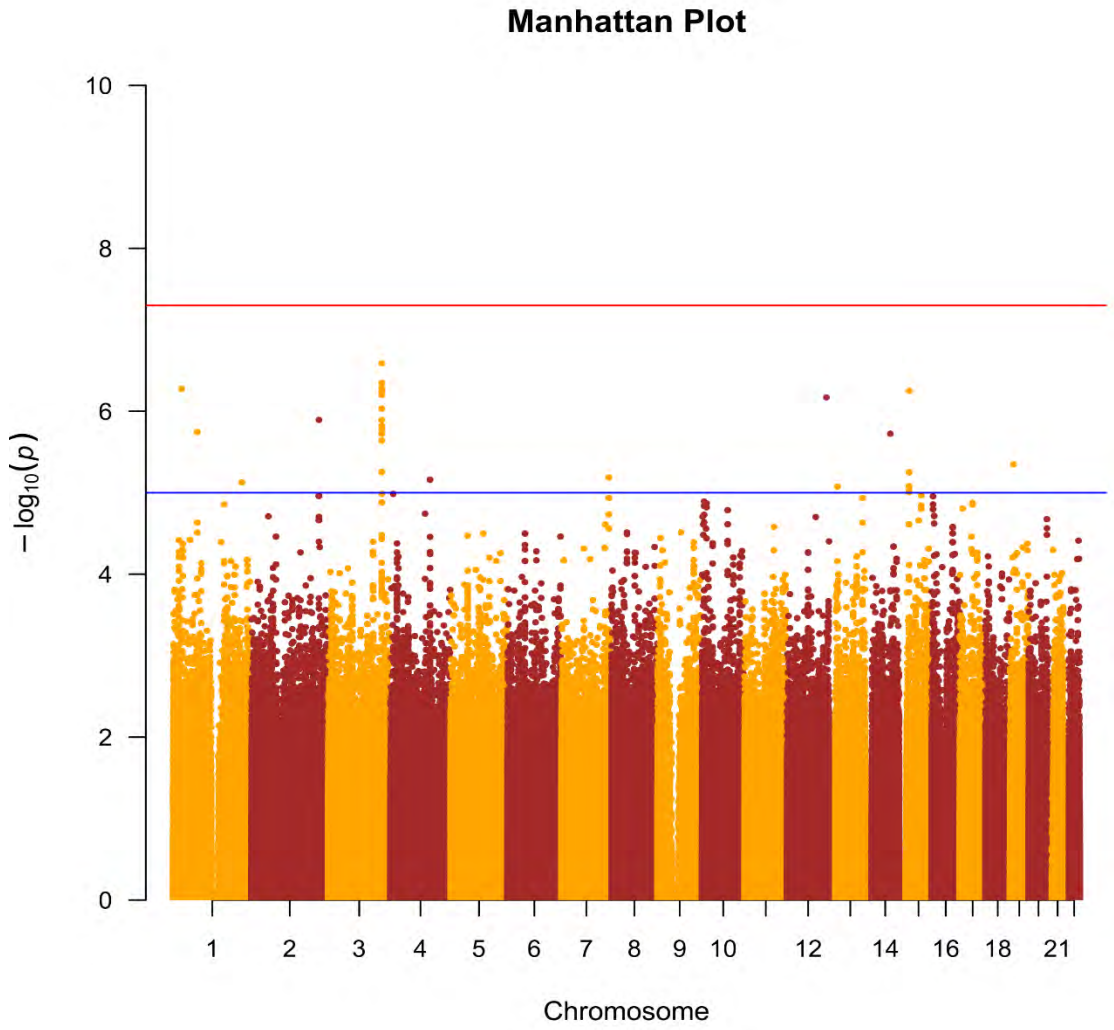
GWAS Results-MDRF Freeze 1



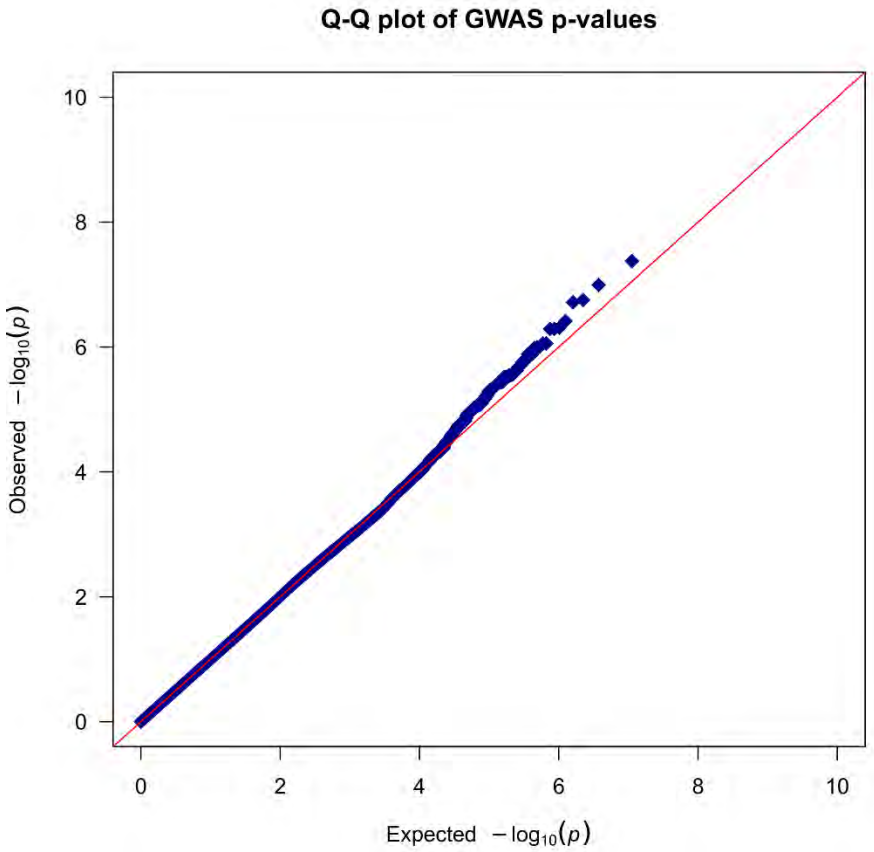


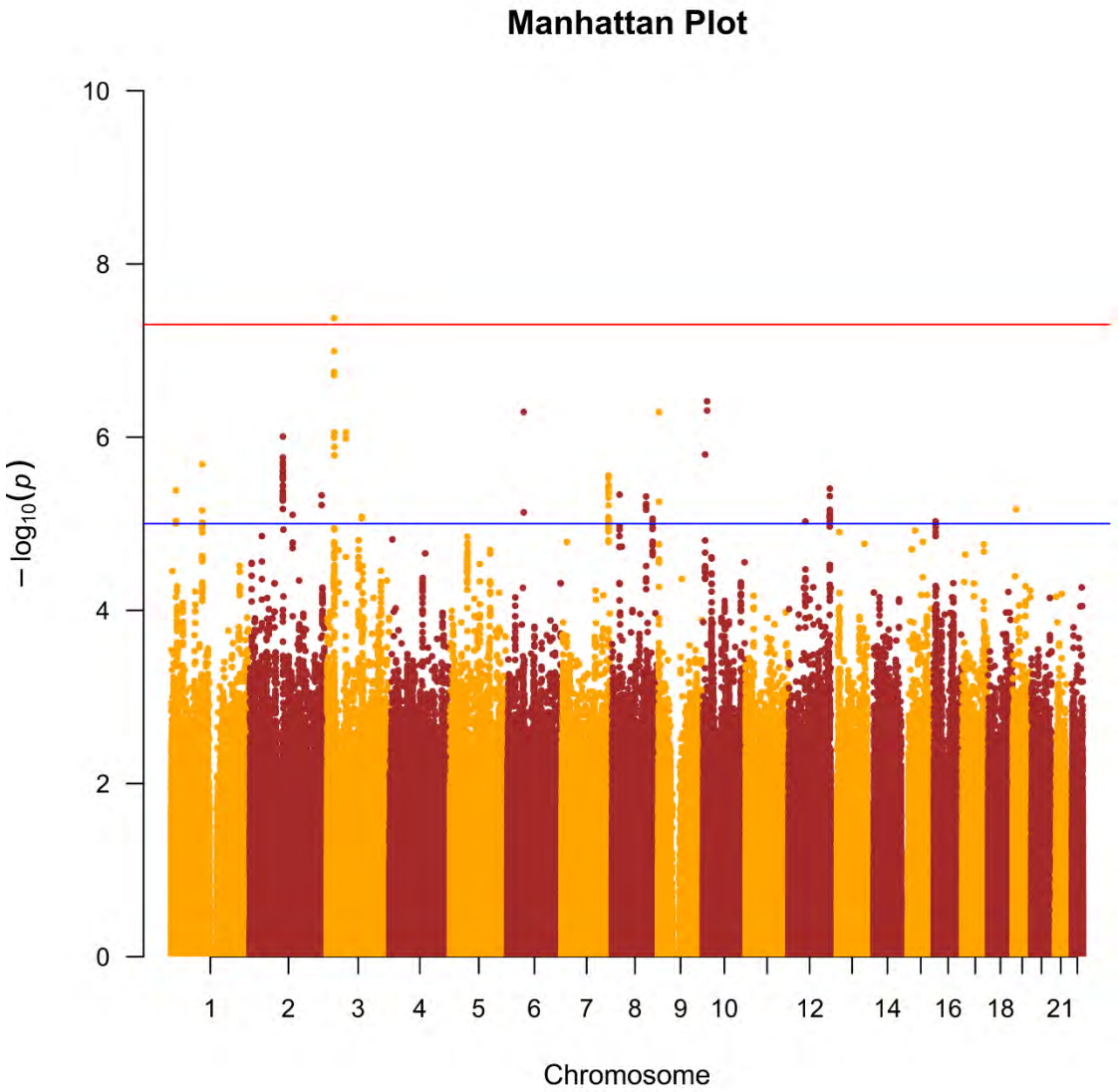
GWAS Results-MDRF Freeze 2





Meta analysis results





Nearest genes

Top Loci

Marker	rsID	Nearest gene(s)	-log$_{10}$(p)
3: 23,351,346		UBE2E2	7.406
10: 13,418,594		AL355870.2	6.415
6: 51,880,345		PKHD1	6.290
9: 2,208,793		SMARCA2	6.288
3: 59,707,773		AC126121.3	6.057
2: 104,275,278		AC018880.2	6.007

UBE2E2 gene (Ubiquitin Conjugating Enzyme E2 E2)

- Shown associated with diabetes- rs7612463- chr3:23294959

Published: 05 September 2010

A genome-wide association study in the Japanese population identifies susceptibility loci for type 2 diabetes at *UBE2E2* and *C2CD4A-C2CD4B*

Toshimasa Yamauchi, Kazuo Hara, [...] Takashi Kadowaki

Nature Genetics **42**, 864–868(2010) | Cite this article

424 Accesses | **187** Citations | **3** Altmetric | Metrics

Medicine (Baltimore). 2016 May; 95(19): e3604. PMCID: PMC4902507

Published online 2016 May 13. doi: 10.1097/MD.0000000000003604 PMID: 27175665

Type 2 Diabetes Risk Allele *UBE2E2* Is Associated With Decreased Glucose-Stimulated Insulin Release in Elderly Chinese Han Individuals

SUMMARY

Summary of analysis

- First study assessing coefficient of failure and its determinants in Asian Indian T2D population.
- Mean annual glycemic deterioration from this study (0.098%) is in range with those estimates from other population.[8,9]
- Indicators of insulin resistance is driving glycemic deterioration in this study population based on final adjusted model [high BMI, Dysplidemia, Low HDL-c]
- We demonstrate the effect of beta cell function and Insulin resistance on glycemic deterioration rate in an age and sex adjusted model.
- Studies conducted among Caucasian population reported similar findings and we validate these findings in Asian Indian population.
- We identified a SNPs in chr 3 associated with glycemic deterioration, which needs validation.
- Combining these phenotypic and genotypic information will aid in development of precision medicine in diabetes management.

Acknowledgment

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- Dr Adem Y Dawed
- Data management team in MDRF
- National Institute for Health Research (NIHR)

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"*The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.*"

THANK YOU

Reference

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