

Genetic Architecture of Type 2 Diabetes in South Indians

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Background

- Diabetes is a complex disease which shows considerable heterogeneity across populations.
- Both, environmental and genetic factors contribute significantly to the aetiology of diabetes.
- South Asians have a four-fold higher risk of developing Type 2 Diabetes (T2D) than Caucasians.¹
- A pilot study on Bangladeshi individuals (n=56) using Whole Exome Sequencing technology showed significant association in the genes *HNF1B* (rs139107479) and *WFS1* (rs71530907) which are associated with diabetes.
- The variant, V25L, of the *HNF1B* gene and A671V, of the *WFS1* gene have earlier been identified in a South Asian population.
- Both the variants have been found to have a very low frequency in European populations.

Fig 1. Frequency of variants in different ethnicities (n=56)

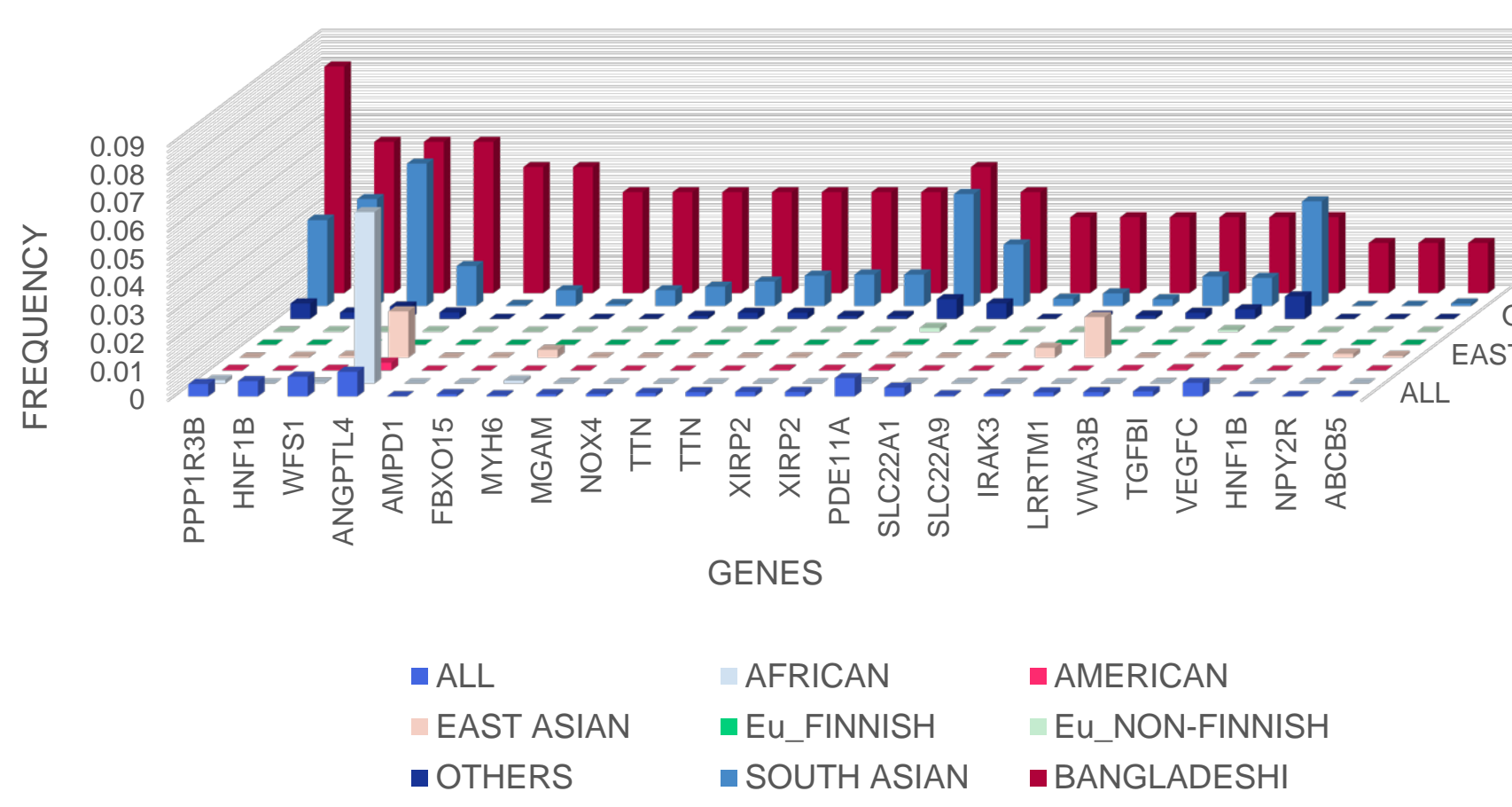


Table 1: Prevalence of T2D in South Asians

- India shows the highest prevalence of Type 2 Diabetes among the South Asian countries.

Countries	No. of people with diabetes in the 20-79 age group (millions)		No. of people with diabetes in the 60-79 age group (millions)	
	Year 2010	Year 2030	Year 2010	Year 2030
India	50.8	87	15.6	31.8
Pakistan	7.15	13.8	1.65	3.56
Bangladesh	5.68	10.4	0.99	2.36
Nepal	0.51	1.07	0.16	0.35
Sri Lanka	1.53	2.16	0.5	1.02
Afghanistan	0.86	1.73	0.2	0.34
Maldives	0.01	0.03	0	0.01

Table 2: Major SNPs found in South Asian GWAS

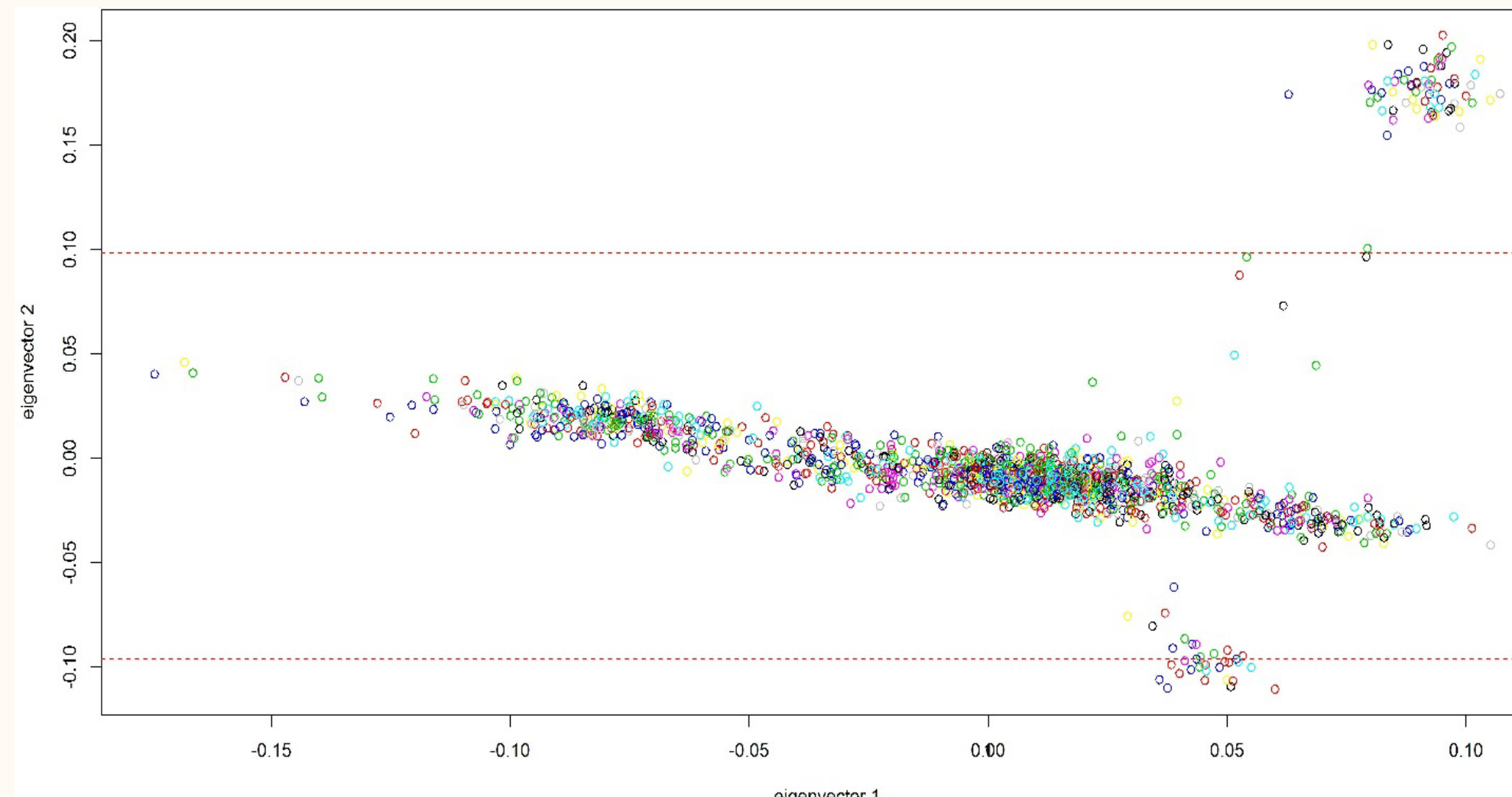
- Several genes have been implicated as a risk factor for Type 2 Diabetes.
- Some of them are as follows:

rsId	Gene	Risk Allele	RAF	OR (95%CI)	p Value-South Asian	p Value-Trans Ethnic
rs7903146	<i>TCF7L2</i>	T	0.31	1.25 (1.19-1.32)	3.60E-19	7.80E-75
rs1801282	<i>PPARG</i>	C	0.87	1.09 (1.00-1.18)	4.10E-02	5.70E-10
rs4402960	<i>IGF2BP2</i>	T	0.42	1.12 (1.07-1.18)	1.90E-06	9.50E-18
rs9936385	<i>FTO</i>	C	0.32	1.07 (1.02-1.13)	1.00E-02	1.20E-12

Preliminary Outcomes

- A pilot study was conducted using Global Screening Array (GSA) v1.0 for the Indian study cohort.
- After quality control, 2,059 samples were considered for further analysis.
- Principal component analysis (PCA) revealed differences within the South Indian genome based on their geographical locations.

Fig 2: Principal component analysis



- Figure 2 highlights three distinct clusters of T2D study participants based on the geographical location within South India.

Aim

The aim of the study is to identify specific causal genetic risk factors and estimate the age of onset of Type 2 Diabetes in a South Indian population.

Objectives

- To validate the genes identified in the pilot study on a larger Bangladeshi population (n=1,700).
- To genotype 20,000 diabetic Indian individuals using Infinium GSA-24 v.1.0 by Illumina.
- To do a quality control and genome wide analysis to identify risk alleles associated with Type 2 Diabetes in South Indians.
- To identify specific MODY mutations using targeted sequencing in an Indian diabetic population (n=1,860).

Study Significance

- This will be the first study comparing genetic determinants of Type 2 Diabetes in a large South Indian and Caucasian population using both genotyping and sequencing.
- Till date, very few studies have looked at a South Indian population. Most have focussed on North West Asia.
- The results of the study will help in understanding missing heritability, familial clustering and heterogeneity of diabetes in South Indians and Caucasians.
- The study could contribute towards developing a reference panel for South Indian specific studies.

References

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Disclaimer: 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.

Methodology

Selection of diabetic specific variants from the pilot Bangladeshi study (n=56)

Validation of the study on a larger population of Bangladeshi individuals (n=1700) living in East London (East London Genes and Health Study)

GWAS on 20,000 Diabetic Individuals from India and do an analysis

Analyse Asian specific Genotyped data from the UK Biobank .

Analyse Targeted Sequencing data from an Indian diabetic population

Identification of frequencies of diabetic specific variants in the South Indian population

Reference panels such as HRC, 1,000 Genomes and 7,000 Whole Genome data from India will be used for imputation.

Comparison of the frequencies with European populations on gNOMAD

Estimate age of onset of Type 2 Diabetes in South Indians.