Genetic Variants Associated with Lower Age of Onset of Type 2 Diabetes in South Indians – A Pilot Study

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INTRODUCTION

- Genetic studies on complex traits focus on phenotypic variations within and between populations.
- Understanding the genetic control of phenotypic variability will aid in developing more effective treatment for diabetes.
- South Asians, have a four fold higher risk of developing diabetes than Caucasians.[1]
- Indians tend to develop diabetes at an early age and are more insulin resistant relative to Caucasians.[2]
- An Ala98Val polymorphism in the Hepatocyte Nuclear Factor- 1α has been associated with early onset Type 2 diabetes in Indians.[3]

AIM

The aim of the study is to identify novel loci associated with age of onset of Type 2 Diabetes (T2D) specific to a South Indian population with respect to a Caucasian population.

STUDY POPULATION

- South Indian Type 2 Diabetes cohort from the Madras Diabetes Research Foundation (MDRF), India, n=2,059.
- Scottish Type 2 Diabetic cohort from the Genetics of Diabetes Audit and Research in Tayside, Scotland (Go-DARTS), n=3,673.

METHODOLOGY

The genotyped and imputed data from the South Indian and Scottish cohort were merged(n=5,732). It contained ~64 million Single Nucleotide Polymorphisms (SNPs).

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Principal Component Analysis (PCA) was done on the merged data.

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The most Indian selective principal component (PC1) was used for the Genome-Wide Association analysis (GWAS) on the merged data.

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Variants which were significantly different in both the populations ($p < 5 \times 10^{-8}$) were taken for further analysis.

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The above variants were then tested for their association with age at onset for Type 2 Diabetes, adjusted for sex, in the South Indian cohort only.

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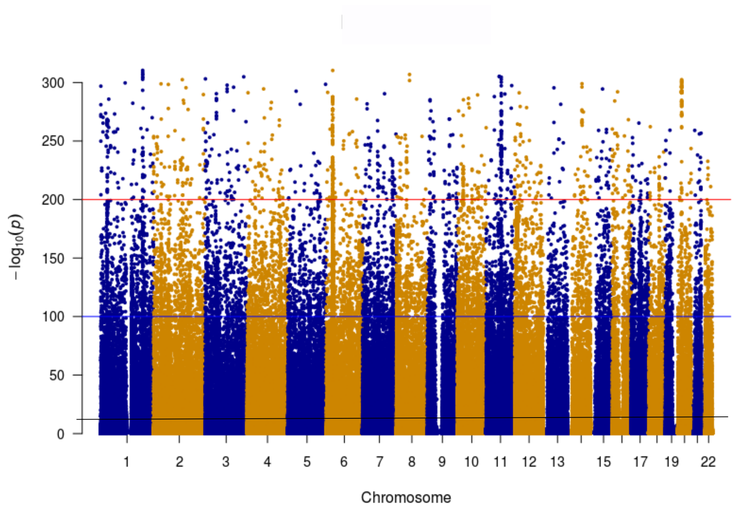
Variants with Info score > 0.60 and Minor Allele Frequency (MAF) >0.05 were considered for analysis.

RESULTS

Figure 1 : Principal Component analysis

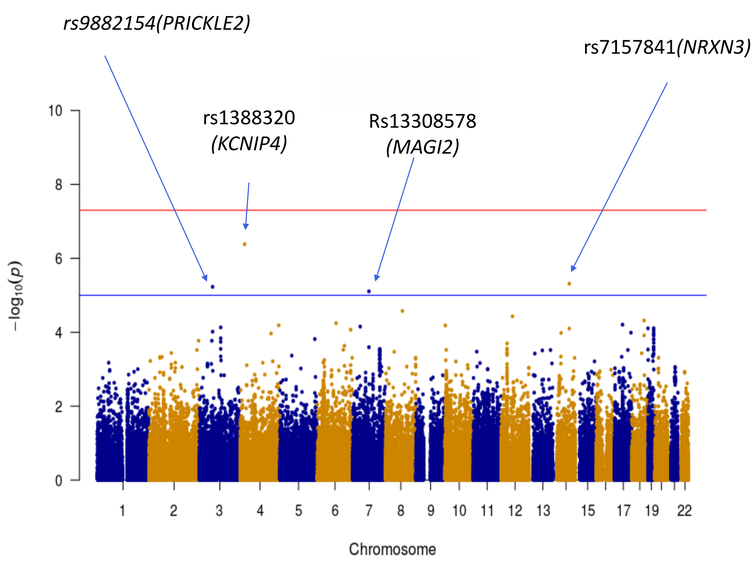
- PCA revealed two distinct populations consisting of Indian and Caucasian ancestry.
- A few individuals from the Go-DARTS group were found to have an Indian ancestry.
- Principal Component 1 (PC1) showed maximum variation between the two populations.

Figure 2: GWAS with most Indian selective principal components on merged data.



- GWAS with the most Indian selective principal component revealed 137,032 variants significantly different in both the populations ($p < 5 \times 10^{-8}$).

Figure. 3 : Age of Onset of Type 2 Diabetes in South India.



RESULTS

Table 1 : Variants associated with age of onset of Type 2 Diabetes in South India

rsid	chr:pos	gene	Ref/alt allele	MDRF MAF	Go-DARTS MAF	MDRF HWE	p value	beta	SE	info score
rs7157841	14:79423452	*NRXN3*	G/A	0.243	0.032	0.0567	4.84E-06	1.55	0.338	0.989
rs9882154	3:64307288	*PRICKLE2*	T/C	0.477	0.288	0.717	5.90E-06	1.38	0.3056	0.945
rs1388320	4:20882591	*KCNIP4*	G/A	0.389	0.32	0.0572	4.15E-07	-1.56	0.307	0.919
rs13308578	7:78408559	*MAGI2*	C/T	0.285	0.463	0.268	7.81E-06	1.55	0.347	0.904

- Four variants were significantly associated with age at onset of T2D ($p < 1 \times 10^{-6}$) in the South Indian population.

CONCLUSION

- All four SNP frequencies differed in the two populations with three of them having a higher frequency in the Indian population.
- Although *NRXN3* (Neuroxin3) is known to be associated with obesity [4], none of the above genes have been associated with Diabetes earlier.
- *KCNIP4* is a potassium voltage-gated channel protein, *PRICKLE2* is involved with neuronal development and function and *MAGI2* is associated with nephrotic syndrome.

WAY FORWARD

- Going ahead, the polymorphisms and genes associated with age at onset of T2D of the Scottish population will be analysed.
- The study will be replicated in bigger cohorts of the two populations for better conclusive evidence.
- Also, the variants significantly different in the two populations will be analysed for their association with other phenotypes.

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