Selection Pressures Affecting Age at Onset of Type 2 Diabetes

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Introduction

- There is compelling evidence that Type 2 Diabetes is strongly influenced by genetic factors.
- Most studies have been done on European populations.
- Since genetic architecture is different between populations, it is important to study the differences.
- Diabetes in India occurs at least two decades earlier in individuals as compared to a UK population.
- One way of identifying the differences in genetic architecture affecting complex traits is by studying the selection pressures affecting genes.

Selection Pressures

- Various factors have shaped evolution across all species.
- Genetic drift, mutation, migration and selection.
- Selection positive or negative, depending on whether it is beneficial or detrimental to the population.
- Fst (F statistics), relies upon the differences in allele frequencies between the populations being studied.

Fixation Index (Fst)



- A certain locus under selection pressure changes its frequency over generations.
- High values of Fst indicate greater genetic differentiation and low values indicate greater genetic similarity.
- Values range from 0 to 1.

STUDY POPULATION

- South Indian diabetes cohort from the Madras Diabetes Research Foundation (MDRF), n=6,056.
- Scottish diabetes cohort from the Scottish Health Research Registry (GoSHARE) study, n=6,681.

METHODOLOGY

- Whole Genome FST was done on 12,737 individuals from MDRF and GoSHARE.
- ~5000 high FST SNPs which had FST > 0.30.
- Association with Age at Onset Phenotype.
- Tests for Selective Sweep Tajima's D and Nucleotide Diversity.
- Locus Zoom
- Conditional Analysis
- Fine Mapping.

PCA



173 individuals of Indian Ancestry were found within the GoSHARE cohort who were removed from further analysis.

AGEONSET



*Adjusted for Sex

GODARTS- GOSHARE

Chr_Pos	rsid	Ref	Alt	MAF_goshareFF	Freq_mdrfFF	beta	se	p.value	hweP_goshareFF	n_studies	effects	Location	Gene
6:32614080	rs9273242	Т	C	0.385	0.82	0.634	0.148	1.95E-05	0.7962	4		intergenic	HLA-DQA1;HLA-DQB1
6:32615510	rs17843577	С	Т	0.394	0.844	0.627	0.148	2.39E-05	0.7009	4		intergenic	HLA-DQA1;HLA-DQB1
6:32615312	rs17612548	А	G	0.395	0.14	0.621	0.149	2.97E-05	0.5908	4		intergenic	HLA-DQA1;HLA-DQB1
5:33951693	rs16891982	С	G	0.035	0.634	2.436	0.615	7.62E-05	1.44E-46	3	+++?	exonic	SLC45A2
6:32628736	rs9273532	С	Т	0.39	0.14	0.576	0.148	9.99E-05	0.9385	4		intronic	HLA-DQB1
6:32615551	rs17843580	А	G	0.387	0.85	0.573	0.148	1.14E-04	0.757	4		intergenic	HLA-DQA1;HLA-DQB1
6:32615421	rs7745002	А	G	0.463	0.903	0.571	0.15	1.36E-04	0.2095	4		intronic	HLA-DQA1
6:32623300	rs9273330	С	Т	0.404	0.853	0.572	0.151	1.49E-04	0.7606	4		intergenic	HLA-DQA1;HLA-DQB1
6:32624731	rs74824383	А	G	0.44	0.882	0.576	0.154	1.84E-04	0.5513	4		intergenic	HLA-DQA1;HLA-DQB1
6:32620359	rs17612802	С	Т	0.39	0.842	0.555	0.148	1.87E-04	0.7188	4		intergenic	HLA-DQA1;HLA-DQB1
6:32615527	rs17843579	Т	G	0.39	0.854	0.55	0.149	2.30E-04	0.9385	4		intergenic	HLA-DQA1;HLA-DQB1
6:32501122	rs76817401	G	Т	0.074	0.516	0.724	0.199	2.70E-04	0.3712	4		intergenic	HLA-DRB5;HLA-DRB6

Chr_Pos	rsid	Ref	Alt	MAF_goshareFF	Freq_mdrfFF	BETA	SE	P_value	hweP_mdrfFF	Location	Gene
2:175090397	rs67654651	G	С	0.054	0.418	-0.723	0.209	5.50E-04	1.85E-01	intronic	OLA1
2:175083689	rs67910840	С	G	0.055	0.415	-0.717	0.211	6.60E-04	7.56E-01	intronic	OLA1
2:175093229	rs66463720	G	A	0.054	0.416	-0.692	0.209	9.40E-04	1.32E-01	intronic	OLA1

LOCUS ZOOM





Conditional Analysis

- Conditioned on the top SNP 6:32614080 (HLA-DQA1) which gave 5:33964210 (SLC45A2) as the next hit.
- Conditioned on both 6:32614080 and 5:33964210 didn't give any other significant hits.

Fine mapping

- Fine mapping was done using the software PAINTOR_v3.
- The analysis includes -
 - Genetic association data from summary statistics LD structure Functional Annotation
- SNPs which were within 100kb of the top hit (50 kb upstream and downstream) were considered for analysis.

Locus 1 - HLA

		_		1
Zscore	Posterior_Prob	chr_pos	p.value	
-1.704581	0.993884	6:32627250	8.83E-02	
-4.272847	0.926952	6:32614080	1.95E-05	•
-3.861015	0.062732	6:32615551	1.14E-04	
-4.227756	0.06068	6:32615510	2.39E-05	
-4.178486	0.0562	6:32615312	2.97E-05	
-2.66083	0.036172	6:32627310	7.81E-03	
-3.795609	0.023072	6:32623300	1.49E-04	
-3.737664	0.022564	6:32620359	1.87E-04	
-3.685656	0.022356	6:32615527	2.30E-04	
-3.742726	0.016792	6:32624731	1.84E-04	
-3.49102	0.014812	6:32615427	4.84E-04	
-3.893139	0.012308	6:32628736	9.99E-05	
-3.306831	0.009988	6:32620976	9.49E-04	
-3.54191	0.004564	6:32607008	4.00E-04	
-2.711439	0.001388	6:32607735	6.72E-03	
-3.817205	0	6:32615421	1.36E-04	
-3.385392	0	6:32612034	7.15E-04	
-3.28178	0	6:32627976	1.04E-03	
-3.226382	0	6:32627992	1.26E-03	
-2.802334	0	6:32612339	5.09E-03	





Individual tests of Association

SNP	Ref	Alt	MAF	beta	se	p-value	n_studies
rs9273242	Т	С	0.385	0.058	0.014	8.02E-05	4

SNP	Ref	Alt	MAF	beta	se	p-value	n_studies
rs9273410	С	A	0.425	0.018	0.015	0.234	4

SNP	Ref	Alt	MAF	beta	se	p-value	n_studies
rs9273242	т	С	0.385	0.058	0.014	8.02E-05	4
rs9273410	С	А	0.425	0.018	0.015	0.235	4

Multi-Tissue eQTL rs9273242

					Single-tissue eQTL	Single-tissue eQTL p-value
Tissue	Samples	NES	p-value	m-value	NES (with 95% CI)	versus Multi-tissue Posterior Probability
Whole Blood	670	-0.758	2.0e-180	1.00	•	
Skin - Sun Exposed (Lower leg)	605	-1.05	3.0e-179	1.00		
Muscle - Skeletal	706	-0.982	6.2e-163	1.00		
Adipose - Subcutaneous	581	-0.980	2.2e-146	1.00		
Thyroid	574	-0.933	1.2e-139	1.00		
Skin - Not Sun Exposed (Suprapubic)	517	-0.953	8.4e-139	1.00 1	•	
Nerve - Tibial	532	-0.927	1.0e-125	1.00 -		
Breast - Mammary Tissue	396	-0.900	3.2e-108	1.00		
Artery - Tibial	584	-0.731	6.6e-107	1.00		
Adipose - Visceral (Omentum)	469	-0.967	3.5e-103	1.00 -		
Esophagus - Mucosa	497	-0.857	1.4e-101	1.00	-	
Esophagus - Muscularis	465	-1.00	4.8e-101	1.00 -		
Lung	515	-0.739	4.0e-91	1.00	-	
Heart - Left Ventricle	386	-0.933	7.0e-84	1.00 -	F I	
Heart - Atrial Appendage	372	-1.04	1.9e-79	1.00 -		
Esophagus - Gastroesophageal Junction	330	-1.01	1.4e-78	1.00 -		
Colon - Transverse	368	-0.771	5.6e-70	1.00	-	
Colon - Sigmoid	318	-0.942	8.7e-67	1.00 -	⊢	
Spleen	227	-0.952	2.4e-64	1.00 -	- 🧧	
Stomach	324	-0.883	2.2e-61	1.00 -	(편	
Pancreas	305	-0.948	8.3e-57	1.00 -	⊢ 14	
Artery - Aorta	387	-0.704	2.2e-55	1.00		0 -
Testis	322	-0.959	4.0e-51	1.00 -	- '8'	
Prostate	221	-0.844	2.7e-47	1.00	<u> </u>	
Pituitary	237	-0.866	2.7e-40	1.00 -		
Brain - Caudate (basal ganglia)	194	-0.787	9.3e-38	1.00	\$	
Brain - Cerebellum	209	-0.864	1.2e-36	1.00 -	5	
Brain - Nucleus accumbens (basal ganglia)	202	-0.839	8.9e-35	1.00	— <mark>—</mark> — 🗖	
Liver	208	-0.790	5.1e-33	1.00	- - ă	
Artery - Coronary	213	-0.740	6.5e-33	1.00	_ 	
Brain - Putamen (basal ganglia)	170	-0.903	6.5e-32	1.00 -	<u> </u>	
Small Intestine - Terminal Ileum	174	-0.721	1.8e-31	1.00		
Cells - EBV-transformed lymphocytes	147	-0.970	7.6e-31	1.00	_	
Vagina	141	-0.974	4.0e-30	1.00	_	
- Brain - Hippocampus	165	-0.771	1.8e-29	1.00	_ _ ,	
Uterus	129	-0.984	3.2e-27	1.00	_ ⁵	
Brain - Hypothalamus	170	-0.787	9.5e-26	1.00	_ <u>_</u>	
Brain - Cerebellar Hemisphere	175	-0.892	3.7e-25	1.00 -	<u> </u>	
Brain - Amyodala	129	-0.770	2.3e-24	1.00		
Minor Salivary Gland	144	-0.923	2.8e-24	1.00	– –	
Brain - Spinal cord (cervical c-1)	126	-0.799	4.2e-23	1.00	_ _	
Brain - Substantia niora	114	-0.852	6.8e-20	1.00 -	- -	
Ovary	167	-0.576	3.1e-18	1.00		
Kidney - Cortex	73	-0.902	1.8e-12	1.00		
Adrenal Gland	233	-0.550	4 5e-11	1.00		
Brain - Anterior cinculate cortex (BA24)	147	-0.612	1.4e-0	1.00		
Brain - Antenor ungulate contex (BA24) Brain - Cortex	205	-0.305	2.40.7	0.00		
Brain - Contex (BAO)	175	-0.288	1.50.4	0.00		Ŏ
Colle - Cultured Shrebitate	400	-0.300	0.74.4	0.00		07
Cells - CultUred Tibroblasts	483	-0.220	2./e-4	0.00		

Single-Tissue eQTL rs9273242

Minor Allele - T



Multi-tissue eQTL – rs9273410

Jaine Jaine <th< th=""><th>Single-tissue eQTL p-value</th></th<>	Single-tissue eQTL p-value
None Elocit 0.00 -0.097 8.4-14 1.00 Sin - Sun Exposed (Lower leg) 665 -9.970 8.4-12 1.00 Maxeler - Susteal 706 -4.841 1.00 - Maxeler - Susteal 706 -4.848 3.1-16 1.00 Sin - Non Exposed (Gupraphic) 517 -4.858 7.6+97 1.00 Sin - Non Exposed (Cupraphic) 517 -4.859 7.6+97 1.00 Dynoid 544 -4.850 3.5+74 1.00 Premary - Think 546 -4.850 3.5+74 1.00 Breat - Mammary Tisus 596 -4.065 3.5+74 1.00 Breaty - Statical (Commun) 469 -4.851 3.3+71 1.00 Breaty - Maxona 467 -4.677 1.00 Breaty - Maxona 467 -4.757 1.00 Breaty - Maxona 467 -4.757 1.00 Damary - Maxona 407 -4.753 1.00	Multi-tissue Posterior Probability
Shn - San Exposed (Lower ing) 603 - 0.970 8.4+124 1.00 Adipose - Solicitameons 551 - 0.880 3.5+11 1.00 Adipose - Solicitameons 551 - 0.880 3.5+7 1.00 Array - Tibal 524 - 0.657 2.4+77 1.00 Array - Tibal 544 - 0.657 2.4+77 1.00 Exoplangar - Maccalaris 465 - 0.881 3.3+71 1.00 Exoplangar - Maccalaris 465 - 0.881 3.3+71 1.00 Harri - Artive Consenty 1.5 Exoplangar - Maccalaris 465 - 0.655 1.00 Harri - Artive Array 1.5 Exoplangar - Maccalaris 465 - 0.658 4.5+2 1.00 	
Match - Skettall 100 -0.880 3.4-118 1.00 Skin - Naces Sam Exposed (Suprepubic) 317 -0.885 7.6+97 1.00 Skin - Naces Sam Exposed (Suprepubic) 574 -0.805 7.6+97 1.00 News - Tobal 532 -0.805 3.5+74 1.00	
Adopea - Subschlandon (Sampanic) 317 - 0.856 7.6-67 1.00 Thryoid 374 - 0.859 9.6-69 1.00 Arev - Thial 322 - 0.868 3.7-69 1.00 Arev - Thial 342 - 0.659 9.6-69 1.00 Arev - Thial 344 - 0.657 2.4-77 1.00 Adopea - Marcalaria 465 - 0.806 3.7-64 1.00 Adopea - Marcalaria 467 - 0.755 2.2-6-77 1.00 Bophaga - Marcalaria 467 - 0.755 2.2-6-77 1.00 Harr - Laft Vemicia 336 - 0.941 6.3-6-77 1.00 Harr - Laft Vemicia 366 - 0.933 4.0-52 1.00 Colos - Signoid 318 - 0.814 6.6-54 1.00 Colos - Signoid 318 - 0.814 6.6-54 1.00 Colos - Signoid 318 - 0.814 6.6-54 1.00 Colos - Signoid 318 - 0.723 3.8-79 1.00 Brain - Candare (baal ganglia) 100	
Skm - Nor Sam Experies (Spragnotic) 517 - 0.38 7 (Ae-97 1.00 Nerve - Tobial 512 - 0.603 3.7e-80 1.00 Adapter - Tobial 514 - 0.667 2.4e-77 1.00 Braar - Mancdarin 465 - 0.800 1.3e-70 1.00 Brophagar - Structural 466 - 0.810 1.3e-70 1.00 Brophagar - Structural 467 - 0.735 2.5e-67 1.00 Heart - Artial Appendage 72 - 0.933 4.0e-55 1.00 Heart - Artial Appendage 72 - 0.933 4.0e-55 1.00 Heart - Artial Appendage 72 - 0.933 4.0e-52 1.00 Heart - Artial Appendage 72 - 0.933 4.0e-52 1.00 Heart - Artial Appendage 72 - 0.933 4.0e-52 1.00 Heart - Artial Appendage 72 - 0.844 1.5e-43 1.00 Brain - Structural 73 - 0.772 2.0e-64 1.0e-53 1.00 Heart - Artial Appendage 72 - 0.844 1.5e-43 1.00 Heart - Artial Appendage 72 - 0.848 1.5e-43 1.00 Heart - Artial Appendage 72 - 0.772 2.0e-83 1.00 Heart - Artial Appendage 72 - 0.772 2.0e-73 1.00 Heart - Artial Appendage 73 - 0.772 2.0e-73 1.00 Heart	
Introd 5/4 -0.83 9.9-8-9 1.00 Arev<- Thial	
Netwer Fundul 392 - 0.000 3. Kesto 1.00 Areay: Think 394 - 0.003 3.5x-74 1.00 Enset: Mammary Time 396 - 0.003 3.5x-74 1.00 Exophages - Mancularis 465 - 0.081 1.3x-70 1.00 Exophages - Mancularis 465 - 0.081 1.3x-70 1.00 Exophages - Mancularis 465 - 0.084 1.5x-57 1.00 Hear: Left Venricle 366 - 0.014 4.6x-54 1.00 Hear: Left Venricle 366 - 0.014 4.6x-54 1.00 Colon: Transverse 368 - 0.700 8.4x-52 1.00 Colon: Signoid 318 - 0.874 3.8x-48 1.00 Colon: Signoid 318 - 0.874 3.8x-48 1.00 Dencess 200 - 0.835 3.3x-39 1.00 Francisco - Construction 200 - 0.835 3.3x-39 1.00 Prostate 221 - 0.772 2.0x-33 1.00 Prostate 200 - 0.818 3.8x-21 1.00 Prostate 200 - 0.818 2.020 0.05 2.11 1.00 Prostate 200 - 0.818 2.020 0.05 0.00 Prostate 200 - 0.818 0.404 0.406 0	
Artery - Alora 1, 1001 944 945 1, 100 Adoptes - Visceral (Consentum) 469 4, 081 3, 38-71 1, 00 Exophagus - Maccoa 467 4, 0.753 2, 24-67 1, 00 Exophagus - Maccoa 467 4, 0.753 2, 24-67 1, 00 Exophagus - Maccoa 467 4, 0.753 2, 24-67 1, 00 Exophagus - Maccoa 467 4, 0.753 2, 24-67 1, 00 Heart - Left Ventricle 364 - 0.404 5, 1, 00 Heart - Atrial Appendage 372 - 0.633 4, 0.64-52 1, 00 Colon - Transverse 368 - 0.700 8, 44-52 1, 00 Colon - Transverse 368 - 0.700 8, 44-52 1, 00 Colon - Transverse 368 - 0.700 8, 44-52 1, 00 Colon - Transverse 368 - 0.700 8, 44-52 1, 00 Colon - Transverse 368 - 0.700 8, 44-52 1, 00 Colon - Transverse 368 - 0.700 8, 44-52 1, 00 Colon - Transverse 368 - 0.707 8, 1, 24-83 1, 00 Frain - Coreselham 209 - 0.533 1, 36-39 1, 00 Frain - Corese (bas) ganglia) 194 - 0.708 6, 64-27 1, 100 Frain - Corese (bas) ganglia) 194 - 0.708 6, 64-27 1, 100 Frain - Corese (bas) ganglia) 194 - 0.708 6, 64-27 1, 100 Frain - Corese (bas) ganglia) 194 - 0.708 6, 64-27 1, 100 Frain - Corese (bas) ganglia) 194 - 0.708 6, 64-27 1, 100 Frain - Corese (bas) ganglia) 194 - 0.708 6, 64-27 1, 100 Frain - Corese (bas) ganglia) 194 - 0.708 6, 52-23 1, 00 Frain - Corese (bas) ganglia) 194 - 0.708 6, 52-23 1, 00 Frain - Corese (bas) ganglia) 194 - 0.708 6, 52-23 1, 00 Frain - Corese (bas) ganglia) 194 - 0.658 1, 22-10 1, 00 Frain - Subtrantia nigra 114 - 0.648 6, 3, 8-13 1, 00 Frain - Mary Gland 144 - 0.672 2, 20-18 1, 00 Frain - Amy glala 109 - 0.653 2, 27-11 1, 00 Frain - Amy glala 109 - 0.653 2, 27-11 1, 00 Frain - Amy glala 109 - 0.653 2, 27-11 1, 00 Frain - Amy glala 114 - 0.648 3, 38-13 1, 00 Adversal Corese (BA24) 147 - 0.5118 4, 56-7 1, 00 Frain - Amy glala cortex (BA24) 147 - 0.5118 4, 56-7 1, 00 Frain - Amy glala cortex (BA24) 147 - 0.513 4, 46-7 1, 00 Frain - Amy glala cortex (BA24) 147 - 0.513 4, 46-7 1, 00 Frain - Ametor classifies cortex (BA24) 147 - 0.513 4, 46-7 1, 00 Frain - Ametor classifies cortex (BA24) 147 - 0.514 1, 46-7 1, 00 Frain - Amotor classifies cortex (BA24) 147	
Bankar - Janimundary 11804 990 4-063 3-54-7 1.00 Esophagua - Mascalaris 445 4-0.80 1.38-70 1.00 Esophagua - Mascalaris 330 -0.941 6-58-75 1.00 Hear - Laft Venticle 336 -0.814 6-56-54 1.00 Colon - Transverse 366 -0.700 8-48-52 1.00 Colon - Sigmoid 318 -0.814 8-0.84-52 1.00 Colon - Sigmoid 318 -0.814 3.88-48 1.00 Spleen 227 -0.864 1.58-43 1.00 Brain - Carobaltum 209 -0.833 1.68-33 1.00 Artey - Aorta 237 -0.798 1.78-33 1.00 Frain - Strate 221 -0.772 2.02-33 1.00 Frain - Strate 221 -0.772 2.02-33 1.00 Frain - Strate (head ganglia) 170 -0.586 1.68-24 1.00 Brain - Carobaltum 129 -0.668 1.38-24 1.00 Frain - Strate 221 -0.772 2.02-33 1.00 Frain - Strate (head ganglia) 170 -0.583 1.62-25 1.00 Frain - Strate (head ganglia) 170 -0.583 1.62-25 1.00 Frain - Strate 129 -0.668 3.82-21 1.00 Frain - Strate (head ganglia) 170 -0.583 1.62-25 1.00 Frain - Strate 129 -0.665 2.58-12 1.00 Gene - Corotact (head ganglia) 170 -0.650 1.18-26 1.00 Frain - Marker - Aorta 129 -0.665 2.58-13 1.00 Frain - Marker - Corotact 120 -0.00 Gene - Corotact 120 -0.00 Frain - Strate Corotact 120 -0.00 Frain - Strate Corotact 120 -0.00 Frain - Strate Corotact 120 -0.00 Gene - Strate 120 -0.065 2.58-13 1.00 Frain - Strate Corotact 120 -0.00 Gene - Strate 140 -0.650 1.18-16 1.00 Frain - Strate Corotact 120 -0.05 -0.212 0.100 Gene - Strate 310 -0.00 Frain - Strate Corotact 120 -0.065 1.18-16 1.00 Frain - Strate Gravita 1-1) 126 -0.646 2.58-18 1.00 Frain - Strate Gravita 1-1) 126 -0.046 1.18-16 1.00 Frain - Amerior Cingulate cortex (BA2) 147 -0.518 4.68-7 1.00 Frain - Strate Gravita 1-1 14 -0.646 3.8-13 1.00 Frain - Strate Gravita 1-1 14 -0	
Adapter Vacuari (Chamman), etc. 4 - 4.84 3.54-71 1.00 Esophagas - Macoa 447 4.753 2.54-67 1.00 Long - Gastroscophageal Junction 330 - 0.441 6.54-57 1.00 Lang - Startoscophageal Junction 330 - 0.441 6.54-57 1.00 Lang - Startoscophageal Junction 330 - 0.441 6.54-57 1.00 Lang - 10.5 - 1	
Bolgmage - Nuscularity 403 - 0.890 1.29-70 1.00 Esophages - Nuscosa 407 - 0.755 2.5e-67 1.00 Hager - Castroesophageal Junction 310 - 0.941 6.5e-57 1.00 Haer - Left Ventricle 386 - 0.814 6.6e-54 1.00 Haer - Left Ventricle 386 - 0.814 6.6e-54 1.00 Haer - Signoid 318 - 0.814 8.4e-52 1.00 Colon - Transverse 366 - 0.700 8.4e-52 1.00 Colon - Signoid 318 - 0.814 3.8e-48 1.00 Haer - Straid Appendage 277 - 0.864 1.5e-43 1.00 Haer - Straid Appendage 327 - 0.864 1.5e-43 1.00 Haer - Straid Appendage 327 - 0.854 1.5e-43 1.00 Haer - Straid Appendage 327 - 0.864 1.5e-43 1.00 Haer - Straid Appendage 327 - 0.772 2.0e-33 1.00 Haer - Straid Appendage 327 - 0.786 1.1e-26 1.00 Haer - Straid Appendage 320 - 0.752 3.3e-24 1.00 Haer - Straid Casal ganglia) 170 - 0.850 3.0e-25 1.00 Haer - Straid Cosal ganglia) 20 - 0.752 3.3e-24 1.00 Haer - Straid Cosal ganglia) 20 - 0.752 3.3e-24 1.00 Haer - Straid Cosal ganglia) 213 - 0.654 3.1e-24 1.00 Haer - Straid Cosal ganglia) 210 - 0.759 1.1e-26 1.00 Haer - Straid Cosal ganglia) 210 - 0.759 2.3e-24 1.00 Haer - Straid Cosal ganglia) 170 - 0.850 3.0e-25 1.00 Haer - Straid Cosal ganglia) 170 - 0.850 3.0e-25 1.00 Haer - Straid Cosal ganglia) 170 - 0.850 3.0e-25 1.00 Haer - Straid Cosal ganglia 120 - 0.752 2.0e-18 1.00 Haer - Straid Cosal ganglia 120 - 0.752 2.0e-18 1.00 Haer - Straid Cosal ganglia 120 - 0.753 2.2e-00 1.00 Haer - Straid Cosal ganglia 120 - 0.753 2.2e-00 1.00 Haer - Straid Cosal ganglia 120 - 0.753 2.2e-00 1.00 Haer - Straid Cosal ganglia 120 - 0.753 2.2e-01 1.00 Haer - Straid Cos - 0.222 2.1e-01 1.00 Haer - Straid Cos - 0.222 2.2e-11 1.00 Haer - Straid Cos - 0.222 2.2e-11 1.00 Haer - Straid Cos - 0.222 2.2e-11 1.00 Haer - 0.200 -	
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-1.0 -0.8 -0.6 -0.4 -0.2 0.0 0.0 0.2	0.4 0.6 0.8

Single tissue eQTL – rs9273410

Minor Allele - C



Locus 2 – SLC45A2

Zscore	Posterior Prob	chr pos	p.value
3.9584	0.99998	5:33951693	7.62E-05
2.378766	0.247496	5:33946571	1.74E-02
-0.962388	0.089668	5:33928902	3.36E-01
2.225757	0.049476	5:33948589	2.61E-02
2.2462	0.041336	5:33952106	2.47E-02
4.175878	0.040108	5:33964210	3.00E-05
0.539553	0.038604	5:33915813	5.90E-01
0.567438	0.037804	5:33923539	5.70E-01
0.555976	0.036132	5:33920667	5.78E-01
0.615744	0.034556	5:33917717	5.38E-01
0.568234	0.034408	5:33922611	5.70E-01
0.538566	0.034312	5:33915935	5.90E-01
3.917014	0.034288	5:33962770	9.05E-05
0.545314	0.034264	5:33921810	5.86E-01
0.604226	0.034252	5:33923272	5.46E-01
0.598419	0.033544	5:33916269	5.50E-01
0.582141	0.033536	5:33922410	5.60E-01
0.541108	0.033096	5:33916434	5.88E-01
0.612774	0.031968	5:33922558	5.40E-01
0.519598	0.031108	5:33917250	6.03E-01
3.69885	0.016364	5:33967145	2.18E-04
2.435579	0.016104	5:33958959	1.49E-02
3.413294	0.015892	5:33964938	6.46E-04
3.479837	0.015596	5:33963333	5.05E-04
3.388511	0.01486	5:33965257	7.07E-04
3.317006	0.01426	5:33955673	9.15E-04
2.48264	0.014212	5:33954880	1.31E-02
1.320506	0.012188	5:33969628	1.87E-01
3.266174	0.011824	5:33951116	1.10E-03
3.050567	0.010936	5:33952378	2.29E-03
3.319983	0.010892	5:33955326	9.05E-04



SLC45A2- rs16891982

- Shows the highest probability of causality.
- Located in the exonic region of the gene.
- Missense variant Leu374Phe
- Has been reported in more than 70 publications.
- Reported for skin, hair and eye pigmentation.
- Has also been reported for skin melanomas.

Tajima's D and Nucleotide Diversity







π

Observed – Expected = π - Φ

Tajima's D > 1 = No sweep Tajima's D = 1 = No selection Tajima's D < 1 = sweep Nucleotide Diversity > 0 = No sweep Nucleotide Diversity = 0 = sweep

TajimasD - HLA

GoShare



MDRF



Nucleotide Diversity - HLA

GoShare





TajimasD - SLC45A2

GoShare





Nucleotide Diversity - SLC45A2





Discussion

- From among ~5000 FST SNPs, 2 regions HLA and SLC45A2 were found to be associated with age at onset of Type 2 Diabetes in the Scottish population.
- Within HLA, two SNPs rs9273242 and rs9273410 showed the highest probability of causality.
- rs9273242 has been known to be associated with Asthma, Celiac disease and hypothyroidism.
- Apart from the above traits, rs9273410 has been associated with Age at which diabetes diagnosed in UK Biobank (p=3.2e-43).
- No selective sweep was observed in the HLA gene in either populations.

- Within SLC45A2, rs16891982 showed the highest probability of causality.
- The region had shown presence of selective sweep in the Scottish population, but not in the Indian population.
- OLA1 region in MDRF, though not highly significant, shows considerable promise.
- It reduces age onset by almost a year and is very frequent in Indians.
- It interacts with BRCA1 and is implicated in breast cancers.
- The region needs to be replicated and further analysis done to better understand its importance.

Thank you