2018 ICDM

Genetic and Epigenetic Research on Type 2 Diabetes in Koreans

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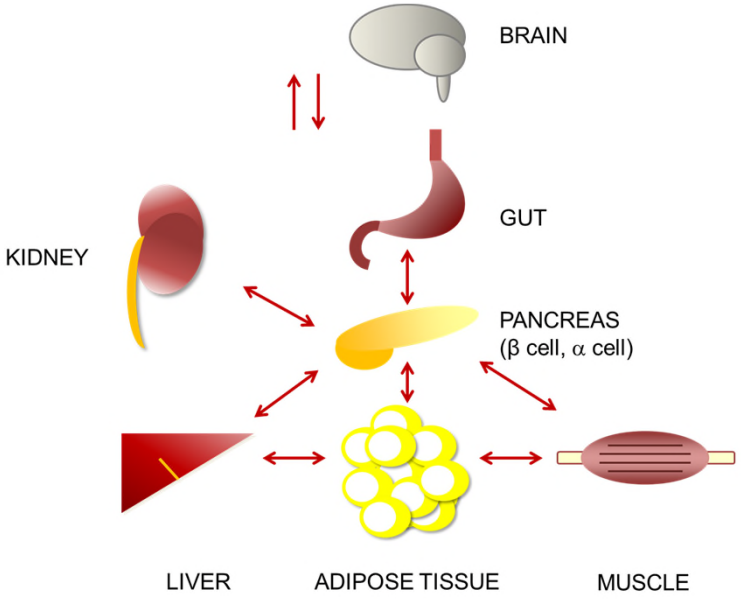
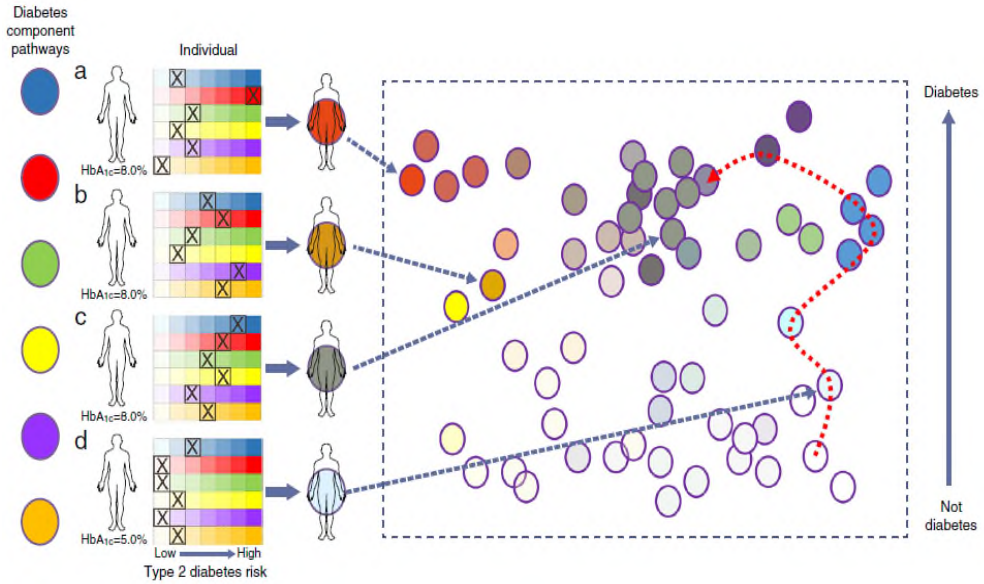
Diverse Pathophysiology of Type 2 Diabetes

Key Pathophysiologic Pathways



'Palette' Model of Diabetes

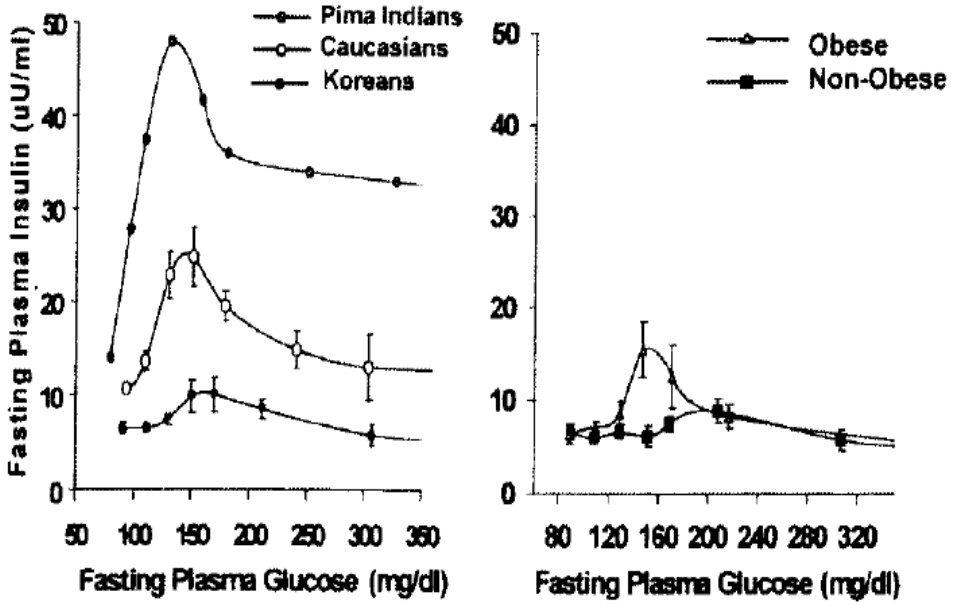


- Type 2 diabetes is a heterogeneous group of disorders characterized by hyperglycemia that results from decreased insulin secretion and/or decreased insulin action
- Multiple pathophysiologic pathways and organs are involved in the development of diabetes

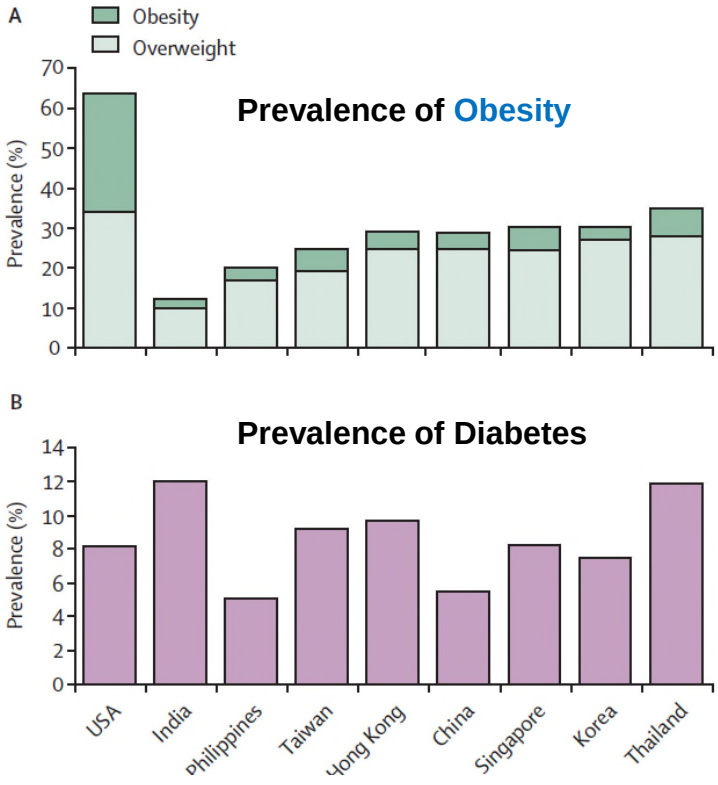
McCarthy MI. Diabetologia 2017

Clinical Heterogeneity of T2D

Decreased Insulin Secretion



Lower BMI in Asian T2D

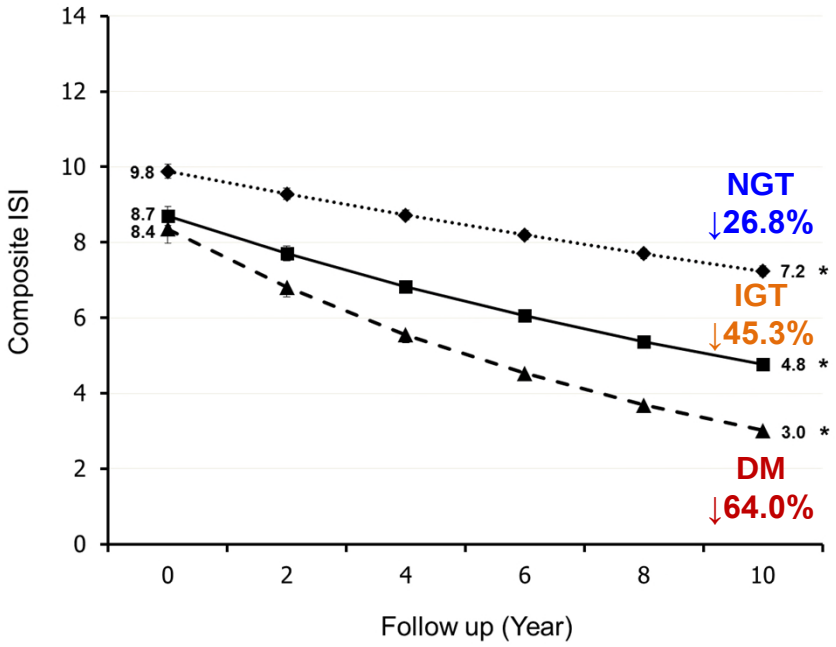


- East Asian type 2 diabetes patients
  - √ are characterized by a decreased insulin secretory capacity
  - √ have lower BMI than European patients

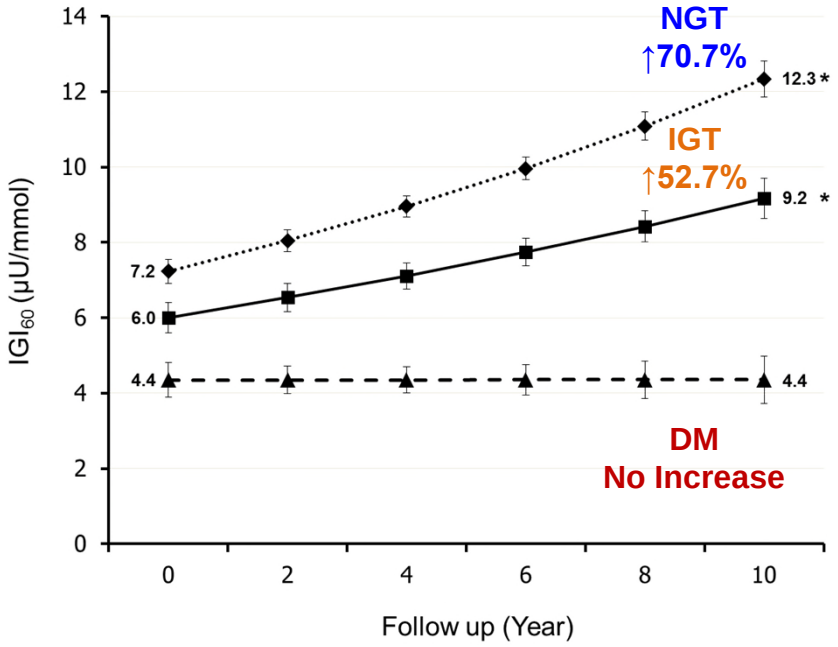
Min HK. Diabetic Medicine 1996
Yoon KH. Lancet 2006

Trajectory of Insulin Sensitivity and Insulin Secretion in 10 Years of Follow-up

Change in Insulin Sensitivity
Composite ISI (Matsuda Idex)



Change in Insulin Secretion
Insulingenic Index (60min)

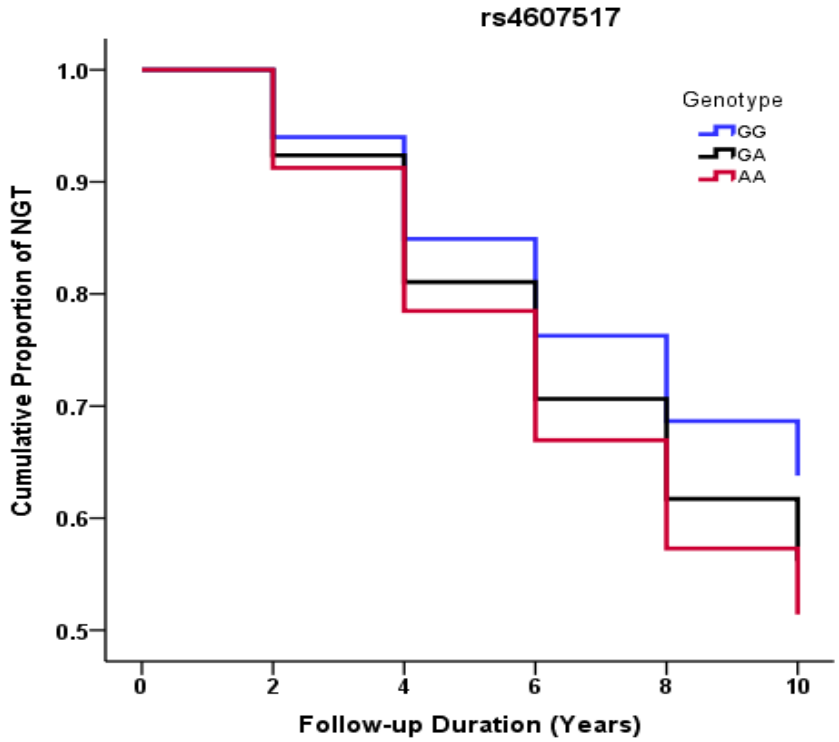


- Decreased beta cell function unable to compensate for the decreased insulin sensitivity is critical in the development of diabetes in Koreans

*p<0.01 for 10 vs. 0 years.

Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Jan 2016

Genetic Variant in Glucokinase



SNP	Nearest Gene	Risk allele	RAF in non-progressor (n=2,046)	Non-Progressor vs. Progressor to Prediabetes/Diabetes			
				RAF in prediabetes or diabetes (n=1,349)	HR	95% CI	p value
rs4607517	***GCK***	**A**	**0·16**	**0·21**	**1·27**	**(1·16 to 1·38)**	**$1·70\times10^{-7}$**

Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Jan 2016

Longitudinal Change in Glucose

Chr	SNP	Locus	A	Independent study						META			ANNOVAR
					Total	Effect	SE	AF	*P*	Type (info)	Weight (direction)	*P* (HetPVal)	
6	rs10947494	34263743	A/G	KARE	6,122	0.213	0.046	0.205	4.53×10^{-06}	imputed (0.992)	10,528 (++)	3.64×10^{-06} (0.1032)	*NUDT3,RPS10-NUDT3* (intronic)
				GENIE	4,406	0.120	0.068	0.200	7.96×10^{-02}	genotyped (1.000)			
10	**rs11187850**	**96068480**	**A/G**	**KARE**	**6,122**	**0.152**	**0.042**	**0.255**	$\mathbf{3.49 \times 10^{-04}}$	**imputed (0.996)**	**10,528 (++)**	$\mathbf{4.85 \times 10^{-08}}$ **(0.3659)**	***PLCE1*** **(intronic)**
				GENIE	**4,406**	**0.266**	**0.063**	**0.250**	$\mathbf{2.45 \times 10^{-05}}$	**imputed (0.996)**			
15	rs2414772	62654213	G/A	KARE	6,122	-0.163	0.039	0.681	3.26×10^{-05}	imputed (0.998)	10,528 (--)	6.30×10^{-06} (0.2719)	*MIR6085*(dist=18876), *MGC15885*(dist=275158) (intergenic)
				GENIE	4,406	-0.134	0.058	0.671	2.14×10^{-02}	imputed (0.985)			
16	rs16959641	58054099	C/G	KARE	6,122	0.222	0.068	0.078	1.09×10^{-03}	imputed (0.954)	10,528 (++)	2.46×10^{-06} (0.6144)	*USB1* (exonic)
				GENIE	4,406	0.366	0.107	0.076	6.00×10^{-04}	genotyped (1.000)			

Linear mixed model

$$FG_{ij} = \left[\beta_0 + \beta_1 Covariates_i + \beta_2 time_{ij} + \beta_3 SNP_i + \beta_4 SNP_i * time_{ij}\right] + \left[U_{0j} + U_{1j} time_{ij} + r_j\right] + \varepsilon_{ij}, \begin{pmatrix} r_j \\ \varepsilon_{ij} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} {\sigma_1}^2 & 0 \\ 0 & {\sigma_2}^2 \end{pmatrix}\right)$$

Kwak SH, et al., Unpublished data

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nature genetics

GWAS of T2D (Asian Genetic Epidemiology Network)

Meta-analysis of genome-wide association studies identifies eight new loci for type 2 diabetes in east Asians

Yoon Shin Cho[1,46], Chien-Hsiun Chen[2,3,46], Cheng Hu[4,46], Jirong Long[5,46], Rick Twee Hee Ong[6,46], Xueling Sim[7,46], Fumihiko Takeuchi[8,46], Ying Wu[9,46], Min Jin Go[1,46], Toshimasa Yamauchi[10,46], Yi-Cheng Chang[11,46], Soo Heon Kwak[12,46], Ronald C W Ma[13,46], Ken Yamamoto[14,46], Linda S Adair[15], Tin Aung[16,17], Qiuyin Cai[5], Li-Ching Chang[2], Yuan-Tsong Chen[2], Yutang Gao[18], Frank B Hu[19], Hyung-Lae Kim[1,20], Sangsoo Kim[21], Young Jin Kim[1], Jeannette Jen-Mai Lee[22], Nanette R Lee[23], Yun Li[9,24], Jian Jun Liu[25], Wei Lu[26], Jiro Nakamura[27], Eitaro Nakashima[27,28], Daniel Peng-Keat Ng[22], Wan Ting Tay[16],

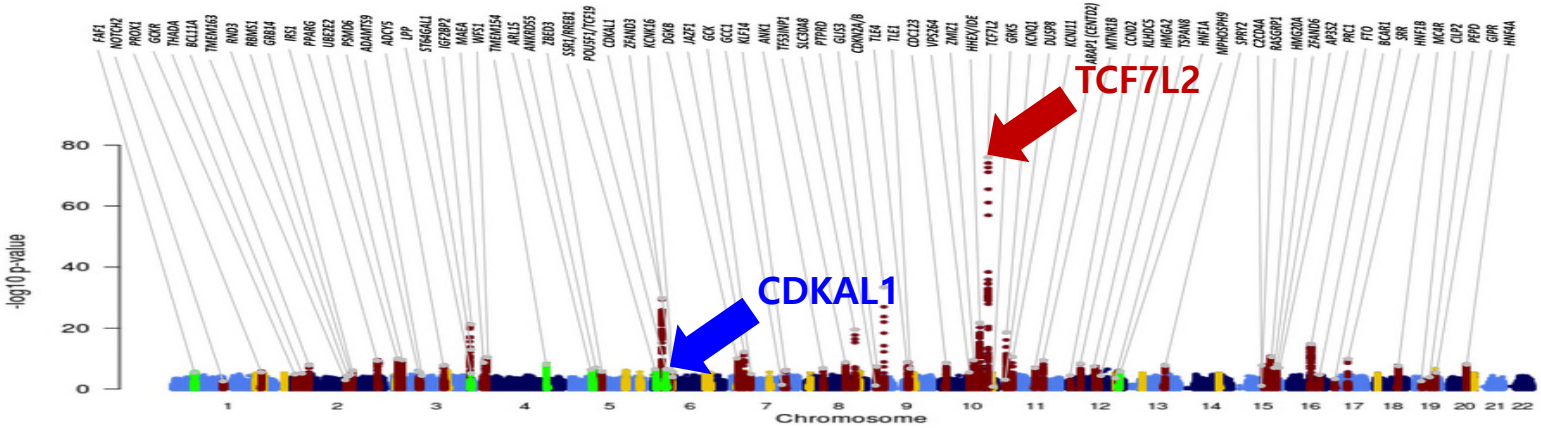
Table 1 Eight new T2D loci reaching genome-wide significance from a combined meta-analysis of stages 1, 2 and 3

SNP	Chr.	Position (bp)	Nearby gene	Risk allele	Other allele	Stage 1 (discovery)[a]		Stage 2 (*in silico* replication)[b]		Stage 3 (*de novo* replication)[c]		Combined (stages 1, 2 and 3)[d]	
						OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Loci showing strong evidence of association with T2D													
rs6815464	4	1,299,901	*MAEA*	C	G	1.09 (1.04–1.14)	8.21×10^{-4}	1.13 (1.07–1.20)	3.67×10^{-5}	1.16 (1.11–1.20)	4.15×10^{-15}	1.13 (1.10–1.16)	1.57×10^{-20}
rs7041847	9	4,277,466	*GLIS3*	A	G	1.09 (1.04–1.14)	1.29×10^{-4}	1.09 (1.03–1.15)	2.20×10^{-3}	1.11 (1.07–1.15)	2.89×10^{-9}	1.10 (1.07–1.13)	1.99×10^{-14}
rs6017317	20	42,380,380	*FITM2-R3HDML-HNF4A*	G	T	1.10 (1.05–1.15)	2.43×10^{-5}	1.07 (0.99–1.15)	8.42×10^{-2}	1.10 (1.06–1.14)	3.96×10^{-7}	1.09 (1.07–1.12)	1.12×10^{-11}
rs6467136	7	126,952,194	*GCC1-PAX4*	G	A	1.12 (1.06–1.18)	6.47×10^{-5}	1.11 (1.04–1.18)	2.09×10^{-3}	1.10 (1.05–1.15)	2.31×10^{-5}	1.11 (1.07–1.14)	4.96×10^{-11}
rs831571	3	64,023,337	*PSMD6*	C	T	1.11 (1.06–1.17)	4.85×10^{-6}	1.06 (1.00–1.13)	4.46×10^{-2}	1.08 (1.05–1.12)	1.41×10^{-5}	1.09 (1.06–1.12)	8.41×10^{-11}
rs9470794	6	38,214,822	*ZFAND3*	C	T	1.11 (1.05–1.17)	1.45×10^{-4}	1.09 (1.02–1.17)	1.48×10^{-2}	1.16 (1.09–1.23)	3.20×10^{-6}	1.12 (1.08–1.16)	2.06×10^{-10}
rs3786897	19	38,584,848	*PEPD*	A	G	1.14 (1.08–1.20)	3.74×10^{-6}	1.05 (0.99–1.12)	1.28×10^{-1}	1.11 (1.04–1.17)	5.46×10^{-4}	1.10 (1.07–1.14)	1.30×10^{-8}
rs1535500	6	39,392,028	*KCNK16*	T	G	1.11 (1.06–1.16)	5.34×10^{-6}	1.07 (1.01–1.15)	3.33×10^{-2}	1.06 (1.02–1.10)	3.50×10^{-3}	1.08 (1.05–1.11)	2.30×10^{-8}
Loci showing moderate evidence of association with T2D													
rs16955379[e]	16	80,046,874	*CMIP*	C	T	1.13 (1.07–1.20)	2.20×10^{-5}	1.10 (1.03–1.17)	6.59×10^{-3}	1.05 (1.01–1.10)	2.19×10^{-2}	1.08 (1.05–1.12)	2.84×10^{-7}
rs17797882	16	77,964,419	*WWOX*	T	C	1.12 (1.05–1.18)	1.76×10^{-4}	1.09 (1.02–1.16)	1.21×10^{-2}	1.06 (1.01–1.11)	1.61×10^{-2}	1.08 (1.05–1.12)	9.49×10^{-7}

[a]Up to 6,952 cases and 11,865 controls. [b]Up to 5,843 cases and 4,574 controls. [c]Up to 12,284 cases and 13,172 controls. [d]Up to 25,079 cases and 29,611 controls. [e]The proxy SNP rs9930117 ($r^2 = 1$) was genotyped in the stage 3 CAGE study.

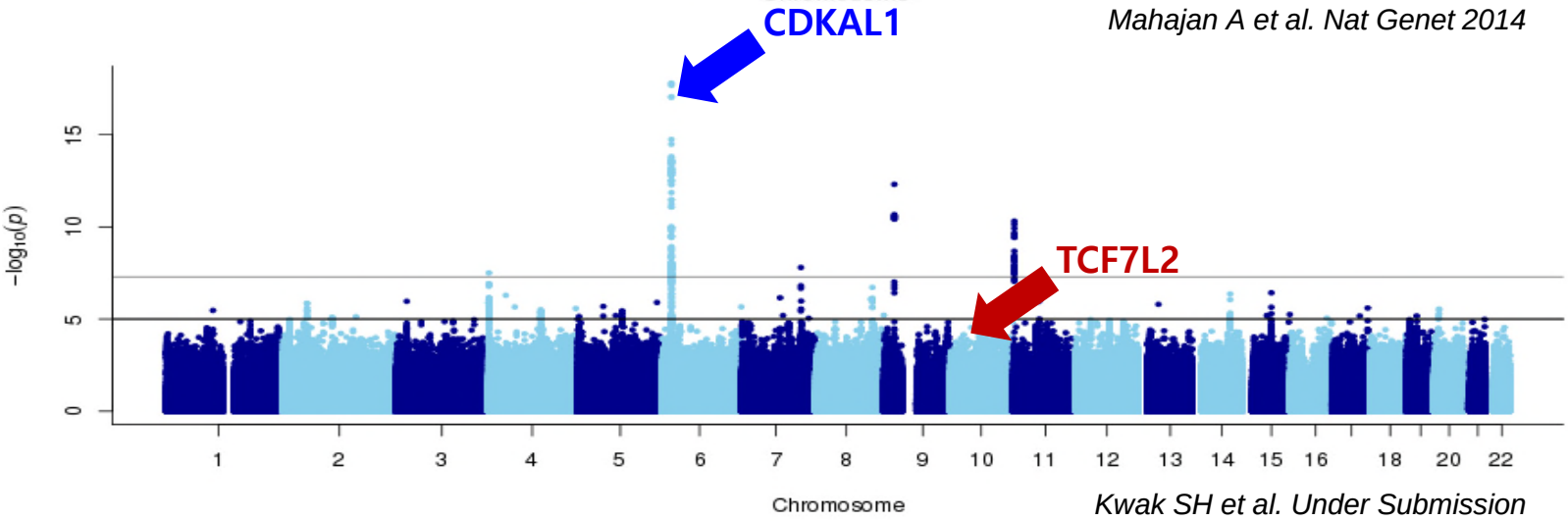
GWAS of T2D
(comparison with Europeans)

European



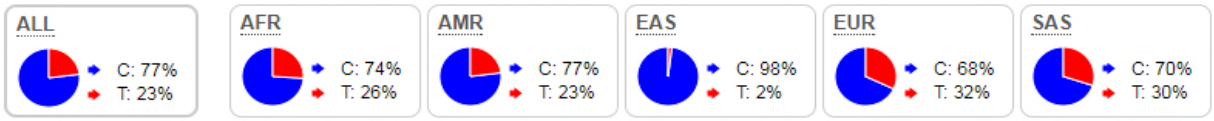
Mahajan A et al. Nat Genet 2014

Korean

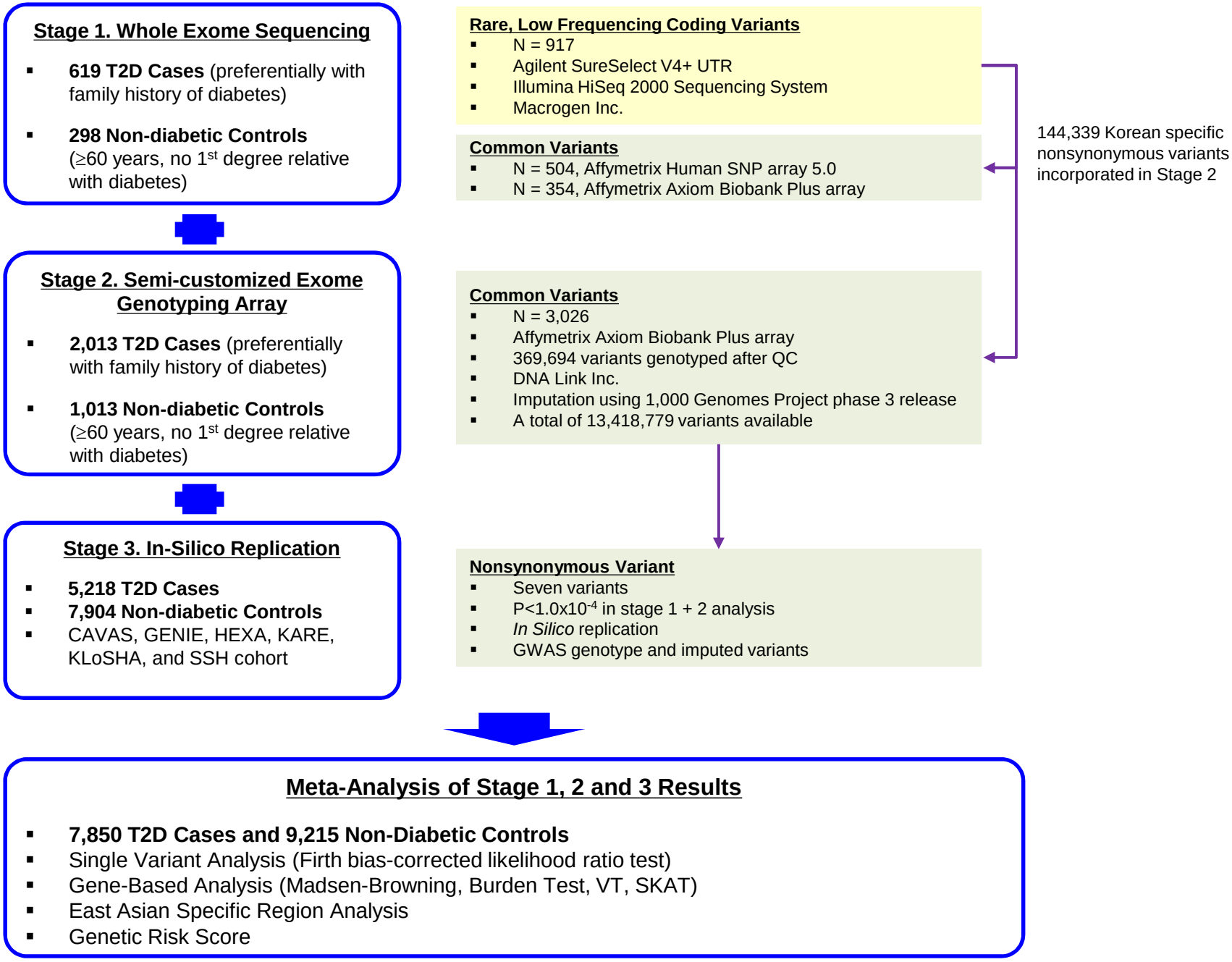


Kwak SH et al. Under Submission

1000 Genomes Project Phase 3 allele frequencies



Study Design



Clinical Characteristics of Participants

	Stage 1 whole exome sequencing			Stage 2 exome array genotyping		
	Type 2 diabetes	**Non-diabetic control**	***P***	**Type 2 diabetes**	**Non-diabetic control**	***P***
N	619	298		2,013	1,013	
Male / Female	287 / 332	133 / 165	0.672	933 / 1080	515 / 498	0.021
Age (years)	56.4 ± 9.1	66.9 ± 7.1	< 0.001	58.4 ± 13.5	65.5 ± 8.3	< 0.001
Onset Age (years)	48.5 ± 10.1	NA	NA	47.0 ± 12.0	NA	NA
BMI (kg/m^2)	24.4 ± 2.8	23.7 ± 3.2	< 0.001	24.3 ± 3.2	23.8 ± 3.0	< 0.001
Systolic BP (mmHg)	127 ± 19	130 ± 20	0.011	129 ± 18	125 ± 16	< 0.001
Diastolic BP (mmHg)	77 ± 10	81 ± 12	< 0.001	78 ± 11	78 ± 10	0.608
HbA1c (%)	8.1 ± 1.8	5.2 ± 0.4	< 0.001	7.7 ± 1.6	5.5 ± 0.3	< 0.001
Fasting Glucose (mg/dl)	152 ± 49	91 ± 6	< 0.001	147 ± 52	90 ± 8	< 0.001
Total cholesterol (mg/dl)	196 ± 41	199 ± 33	0.218	178 ± 40	194 ± 35	< 0.001
Triglyceride (mg/dl)	163 ± 128	129 ± 74	< 0.001	149 ± 94	118 ± 65	< 0.001
HDL cholesterol (mg/dl)	48 ± 12	46 ± 16	0.123	48 ± 14	53 ± 14	< 0.001
LDL cholesterol (mg/dl)	118 ± 33	128 ± 30	< 0.001	104 ± 34	120 ± 32	< 0.001
Insulin Treatment (%)	26.8 %	NA	NA	23.8 %	NA	NA
Lipid Medication (%)	21.0 %	0.0 %	< 0.001	27.5 %	2.7 %	< 0.001
Hypertension Medication (%)	36.7 %	7.0 %	< 0.001	32.0 %	10.0 %	< 0.001

Data are expressed as the mean ± S.D. or percent (%). NA, not applicable. Type 2 diabetes patients with family history of diabetes were preferentially enrolled.

Association results for overall common variants

Chr	Position (hg19)	Ref/ Alt	Gene	AF	Meta-Analysis		Whole Exome Sequencing				Exome Chip			
					OR 95% CI	*P*	OR 95% CI	*P*	AF Case	AF Control	OR 95% CI	*P*	AF Case	AF Control
6	**20,674,691**	**C/T**	***CDKAL1***	**0.508**	**1.57 (1.42-1.74)**	**1.60×10^{-18}**	**1.88 (1.48-2.39)**	**1.49×10^{-7}**	**0.558**	**0.416**	**1.51 (1.35-1.69)**	**1.39×10^{-13}**	**0.544**	**0.431**
9	**22,132,076**	**A/G**	***CDKN2A/B***	**0.375**	**0.68 (0.61-0.75)**	**4.96×10^{-13}**	**0.52 (0.40-0.67)**	**3.25×10^{-7}**	**0.317**	**0.457**	**0.72 (0.64-0.80)**	**1.11×10^{-8}**	**0.350**	**0.432**
11	**2,839,751**	**C/T**	***KCNQ1***	**0.355**	**0.70 (0.63-0.78)**	**4.88×10^{-11}**	**0.74 (0.57-0.94)**	**0.015**	**0.321**	**0.401**	**0.69 (0.61-0.78)**	**7.32×10^{-10}**	**0.329**	**0.414**
7	**127,253,550**	**C/T**	***PAX4***	**0.085**	**1.79 (1.46-2.19)**	**1.60×10^{-8}**	**2.56 (1.58-4.14)**	**5.18×10^{-5}**	**0.119**	**0.056**	**1.66 (1.33-2.07)**	**3.81×10^{-6}**	**0.094**	**0.059**
4	**1,244,218**	**G/A**	***MAEA***	**0.310**	**0.74 (0.66-0.82)**	**3.15×10^{-8}**	**0.85 (0.66-1.08)**	**0.176**	**0.297**	**0.345**	**0.72 (0.63-0.81)**	**3.57×10^{-8}**	**0.286**	**0.356**
11	55,966,855	C/T	*OR5J2*	0.056	0.53 (0.42-0.67)	1.17×10^{-7}	0.39 (0.22-0.71)	0.002	0.039	0.062	0.57 (0.44-0.73)	8.90×10^{-6}	0.048	0.076
8	121,510,827	A/G	*MTBP*	0.075	0.61 (0.50-0.73)	1.91×10^{-7}	0.69 (0.43-1.10)	0.120	0.054	0.086	0.59 (0.48-0.73)	6.22×10^{-7}	0.066	0.099
14	81,611,606	C/T	*TSHR*	0.238	1.38 (1.22-1.56)	4.33×10^{-7}	1.44 (1.07-1.93)	0.016	0.258	0.223	1.36 (1.19-1.56)	5.83×10^{-6}	0.253	0.201

OR and *P* values are from T2D association testing results for alternative allele adjusted for age, sex, and principle components. Stage 1 and 2 association were analyzed with Firth bias-corrected likelihood ratio test. Meta-analysis was done using METAL with inverse variance weighted method under a fixed effects model. Alleles are aligned to the forward strand of the Human Genome Version 19 (hg19). Alt, alternative allele; AF, allele frequency; Chr, chromosome; CI, confidence interval; OR, odd ratio; Ref, reference allele.

Kwak SH et al., Diabetes Sep 2018

Nonsynonymous Variants of T2D (P <1.0×10^{-4})

Chr	Position (hg19)	Ref/ Alt	Gene	Variant	KOR AF	EUR AF	Meta-analysis		Stage 1 whole exome sequencing				Stage 2 exome array genotyping			
							OR (95% CI)	P	OR (95% CI)	P	T2D AF	Control AF	OR (95% CI)	P	T2D AF	Control AF
7	127,253,550	C/T	***PAX4******	rs2233580 Arg192His	0.086	***0.000***	**1.81 (1.64-2.01)**	**6.36×10^{-9}**	2.62 (1.64-4.18)	1.73×10^{-5}	0.122	0.057	1.67 (1.33-2.08)	3.13×10^{-6}	0.094	0.059
4	1,349,029	G/A	***UVSSA****,†	rs2276904 Arg391His	0.376	***0.031***	**0.79 (0.75-0.84)**	**1.03×10^{-5}**	0.91 (0.72-1.15)	0.441	0.363	0.393	0.77 (0.68-0.86)	5.52×10^{-6}	0.357	0.417
6	39,033,595	G/A	***GLP1R****	rs3765467 Arg131Gln	0.211	***0.001***	**0.77 (0.69-0.87)**	**3.72×10^{-5}**	0.74 (0.55-0.98)	0.036	0.196	0.258	0.78 (0.69-0.90)	3.59×10^{-4}	0.198	0.234
12	71,533,622	C/T	***TSPAN8***	rs79443892 Gly44Ser	0.157	***0.018***	**0.76 (0.71-0.81)**	**5.24×10^{-5}**	0.68 (0.51-0.92)	0.011	0.137	0.188	0.78 (0.67-0.91)	1.21×10^{-4}	0.146	0.183
19	18,123,738	T/C	***ARRDC2***	rs7259041 Leu391Pro	0.251	0.254	0.79 (0.75-0.84)	6.19×10^{-5}	0.90 (0.69-1.17)	0.424	0.239	0.268	0.77 (0.68-0.87)	4.97×10^{-5}	0.236	0.280
11	2,869,129	G/A	***KCNQ1****	rs1800172 Gly643Ser	0.053	***0.000***	**0.64 (0.58-0.72)**	**7.51×10^{-5}**	0.73 (0.44-1.21)	0.217	0.048	0.055	0.63 (0.49-0.80)	1.58×10^{-4}	0.046	0.068
10	64,974,537	A/T	***JMJD1C***	rs10761725 Ser464Thr	0.430	0.778	**1.23 (1.17-1.30)**	**8.17×10^{-5}**	1.34 (1.05-1.71)	0.016	0.460	0.379	1.21 (1.08-1.36)	1.22×10^{-4}	0.443	0.401

OR and P values are from T2D association testing results for alternative alleles adjusted for age, sex, and principle components. Stage 1 and 2 association were analysed with the Firth bias-corrected likelihood ratio test. Meta-analysis was performed using METAL with the inverse variance weighted method under a fixed effects model. Alleles are aligned to the forward strand of the Human Genome Version 19 (hg19). Alt, alternative allele; AF, allele frequency; Chr, chromosome; CI, confidence interval; EUR, Europeans; KOR, Koreans; OR, odds ratio; Ref, reference allele. *These genes are located in previously confirmed East Asian T2D GWAS regions. The genome-wide significance threshold was set to $P < 5.0\times10^{-8}$. The Bonferroni corrected significance threshold for variants located in East Asian GWAS regions was set to $P < 6.5\times10^{-5}$ (0.05/770). †These two variants were in modest LD ($r^2 = 0.24$).

Characteristics and genotyping of stage 3 studies (N=13,122)

Study Name	N		Male / Female	Age (years)	Body Mass Index (kg/m2)	HbA1c (%)	Fasting Plasma Glucose (mg/dl)	Diagnostic Criteria	GWAS Chip Platform
CAVAS	1,592	Cases	374 / 435	58.5 ± 7.2	25.3 ± 3.2	NA	146 ± 54	Previous diagnosis of diabetes, fasting glucose ≥ 126 mg/dL	Affymetrix Genome-Wide Human SNP Array 6.0
		Controls	373 / 410	63.6 ± 4.3	23.9 ± 3.2	NA	88 ± 8	No previous history of diabetes, fasting glucose < 100 mg/dL	
GENIE	3,004	Cases	807 / 448	53.0 ± 10.0	23.7 ± 3.1	6.2 ± 1.0	114 ± 31	Clinically diagnosed as T2D using American Diabetes Association criteria.	Korena Chip Version 1.0
		Controls	871 / 878	53.4 ± 6.5	22.5 ± 2.7	5.4 ± 0.2	91 ± 6	Age ≥ 45 years old. No previous history of diabetes. Fasting plasma glucose < 100 mg/dL. HbA1c < 5.7%.	
HEXA	3,158	Cases	203 / 115	58.6 ± 8.0	24.8 ± 2.9	NA	137 ± 62	Previous diagnosis of diabetes, fasting glucose ≥ 126 mg/dL	Affymetrix Genome-Wide Human SNP Array 6.0
		Controls	1,120 / 1,720	52.2 ± 8.1	23.7 ± 2.8	NA	87 ± 7	No previous history of diabetes, fasting glucose < 100 mg/dL	
KARE	4,708	Cases	1,263 / 1,153	63.7 ± 9.0	24.9 ± 3.4	6.7 ± 1.3	120 ± 40	Clinically diagnosed as T2D using American Diabetes Association criteria.	Affymetrix Genome-Wide Human SNP Array 5.0
		Controls	1,006 / 1,286	61.7 ± 8.1	24.0 ± 2.9	5.4 ± 0.3	88 ± 6	Age ≥ 60 years old. No previous history of diabetes. Fasting plasma glucose < 100 mg/dL. HbA1c < 6.0%.	
KLoSHA	211	Cases	47 / 42	75.3 ± 8.2	25.6 ± 3.4	7.4 ± 1.0	145 ± 42	Clinically diagnosed as T2D using American Diabetes Association criteria.	Korena Chip Version 1.1
		Controls	80 / 42	76.8 ± 9.3	23.2 ± 3.5	5.5 ± 0.3	90 ± 6	No previous history of diabetes. Fasting plasma glucose < 100 mg/dL. HbA1c < 6.0%.	
SSH	449	Cases	200 / 131	52.8 ± 10.9	NA	7.8 ± 1.9	162 ± 57	Hospital diagnosis based on American Diabetes Association criteria.	Affymetrix NSP 250K
		Controls	43 / 75	42.8 ± 10.3	NA	5.1 ± 0.3	93 ± 8	No previous history of diabetes, fasting glucose < 100 mg/dL, HbA1c < 5.7%.	

Data are expressed as the mean ± S.D. or percent (%). NA, not applicable.

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Validation of Nonsynonymous Variants of T2D

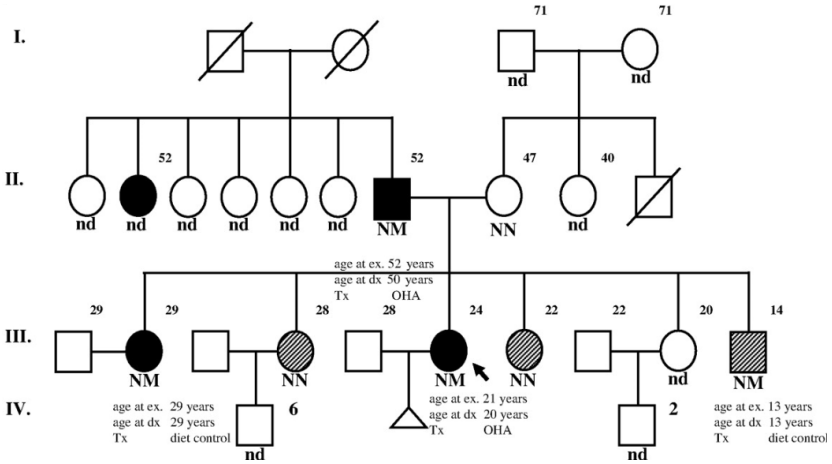
Chr	Position (hg19)	Alleles (Ref, Alt)	Gene	HGVS (rsID)	Korean AF	European AF	Study	OR 95% CI	*P*	AF Case	AF Control
7	127,253,550	C, T	***PAX4***	**p.Arg192His (rs2233580)**	0.086	0.000	Stage 1. WES	2.62 (1.64 - 4.18)	1.73×10^{-5}	0.122	0.057
							Stage 2. Exome Chip	1.67 (1.33 - 2.08)	3.16×10^{-6}	0.094	0.059
							Stage 3. Replication	1.40 (1.26 - 1.56)	9.22×10^{-10}	-	-
							Meta-Analysis	**1.48 (1.35 - 1.63)**	**4.47×10^{-16}**	-	-
6	39,033,595	G, A	***GLP1R***	**p.Arg131Gln (rs3765467)**	0.211	0.001	Stage 1. WES	0.74 (0.55 - 0.98)	0.036	0.196	0.258
							Stage 2. Exome Chip	0.78 (0.69 - 0.90)	3.60×10^{-4}	0.198	0.234
							Stage 3. Replication	0.87 (0.81 - 0.93)	5.77×10^{-5}	-	-
							Meta-Analysis	**0.84 (0.80 - 0.90)**	**3.55×10^{-8}**	-	-
4	1,349,029	G, A	*UVSSA*	p.Arg391His (rs2276904)	0.376	0.031	Stage 1. WES	0.91 (0.72 - 1.15)	0.441	0.363	0.393
							Stage 2. Exome Chip	0.77 (0.68 - 0.86)	5.52×10^{-6}	0.357	0.417
							Stage 3. Replication	0.94 (0.89 - 1.00)	0.038	-	-
							Meta-Analysis	0.91 (0.86 - 0.95)	8.36×10^{-5}	-	-
10	64,974,537	A, T	*JMJD1C*	p.Ser464Thr (rs10761725)	0.430	0.778	Stage 1. WES	1.34 (1.05 - 1.71)	0.016	0.460	0.379
							Stage 2. Exome Chip	1.21 (1.08 - 1.36)	0.001	0.443	0.401
							Stage 3. Replication	1.07 (1.01 - 1.13)	0.014	-	-
							Meta-Analysis	1.11 (1.05 - 1.16)	6.14×10^{-5}	-	-
19	18,123,738	T, C	*ARRDC2*	p.Leu391Pro (rs7259041)	0.251	0.254	Stage 1. WES	0.90 (0.69 - 1.17)	0.424	0.239	0.268
							Stage 2. Exome Chip	0.77 (0.68 - 0.87)	4.97×10^{-5}	0.236	0.280
							Stage 3. Replication	0.95 (0.89 - 1.02)	0.149	-	-
							Meta-Analysis	0.91 (0.85 - 0.96)	0.001		
11	2,869,129	G, A	*KCNQ1*	p.Gly643Ser (rs1800172)	0.053	0.000	Stage 1. WES	0.73 (0.44 - 1.21)	0.217	0.048	0.055
							Stage 2. Exome Chip	0.63 (0.49 - 0.80)	1.58×10^{-4}	0.046	0.068
							Stage 3. Replication	0.99 (0.86 - 1.13)	0.835	-	-
							Meta-Analysis	0.84 (0.74 - 0.95)	0.006		
12	71,533,622	C, T	*TSPAN8*	p.Gly44Ser (rs79443892)	0.157	0.018	Stage 1. WES	0.68 (0.51 - 0.92)	0.011	0.137	0.188
							Stage 2. Exome Chip	0.78 (0.67 - 0.91)	0.001	0.146	0.183
							Stage 3. Replication	1.07 (1.00 - 1.15)	0.062	-	-
							Meta-Analysis	0.98 (0.92 - 1.05)	0.582		

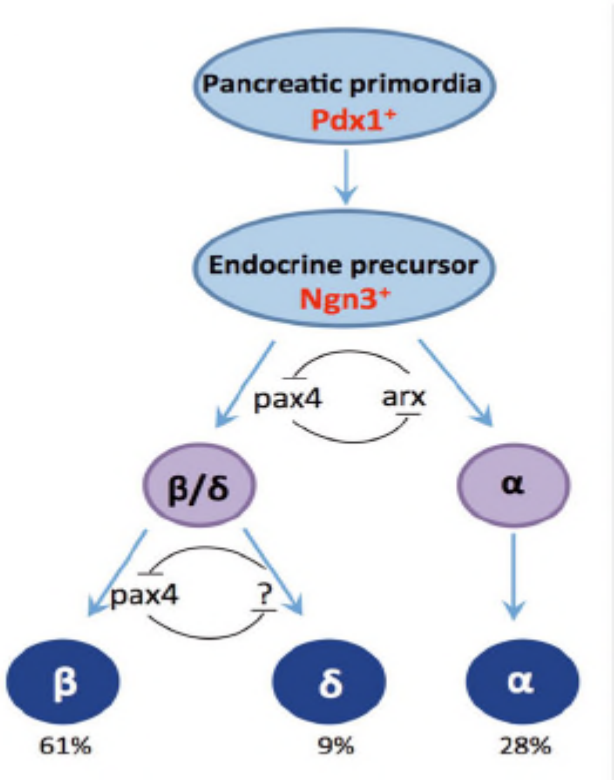
OR and *P* values are from T2D association testing results for alternative alleles adjusted for age, sex, and principle components. Stage 1, 2, and 3 association were analysed with the Firth bias-corrected likelihood ratio test. Meta-analysis was performed using METAL with the inverse variance weighted method under a fixed effects model. Alleles are aligned to the forward strand of the Human Genome Version 19 (hg19). Alt, alternative allele; AF, allele frequency; Chr, chromosome; CI, confidence interval; EUR, Europeans; HGVS, Human Genome Variation Society nomenclature; OR, odds ratio; Ref, reference allele; rsID, dbSNP reference ID. The genome-wide significance threshold was set to $P < 5.0\times10^{-8}$.

CONTENTS

PAX4 (Paired Box 4)

- Plays an important role in the differentiation and development of pancreatic islet beta cells
- Protects adult islets from stress-induced apoptosis
- Promotes differentiation and proliferation of β-cells through MafA repression
- GWAS signal near PAX4
- Reported as a MODY 9 gene in Thais





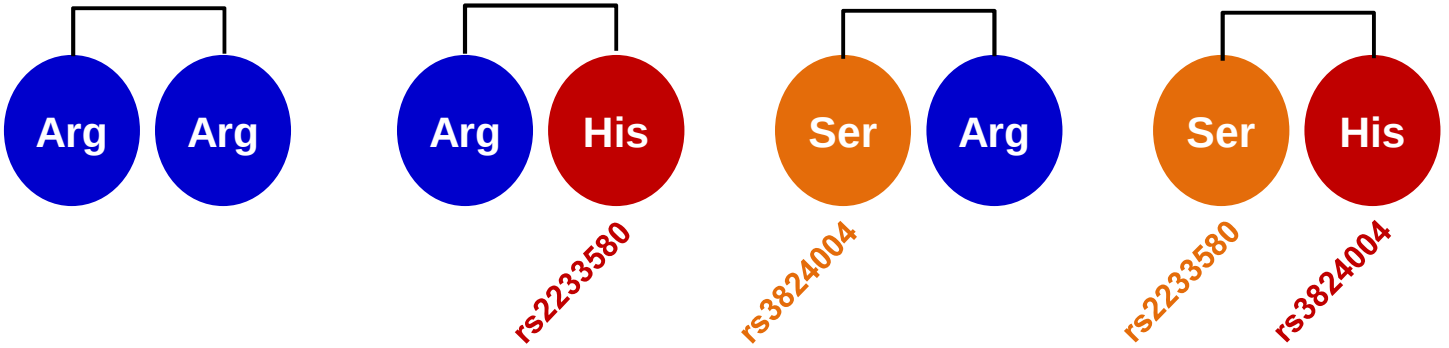
PAX4 favors β-cell lineage development and its absence leads to loss of β and δ-cells

PAX4 Haplotype Association

CHR	SNP1	SNP2	Haplotype	AA	Group	Frequency	OR	*P*
7	rs2233580-C 127,253,550	rs3824004-G 127,253,551	**ACG**	Arginine	Positive Charge	0.874	Ref	Ref
7	**rs2233580-T** **127,253,550**	rs3824004-G 127,253,551	**ATG**	Histidine	Positive Charge	0.086	1.81	6.36×10^{-9}
7	rs2233580-C 127,253,550	**rs3824004-T** **127,253,551**	**ACT**	Serine	Polar Uncharged	0.044	1.62	5.18×10^{-4}
7	**rs2233580-T** **127,253,550**	**rs3824004-T** **127,253,551**	**ATT**	Asparagine	Polar Uncharged	0.000	-	-

LD measure for two SNPs: R-sq 0.002, D'=0.619

Possible Amino Acid Changes



Dosage **0** **1** **1** **2**

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PAX4 Diplotype Analysis

❖ Amino acid variation in the PAX4 192 codon and risk of T2D

PAX4 192 codon	Number of mutant codons	T2D		Non-diabetic control		OR	95% CI	*P*
		N	%	N	%			
Arg/Arg	0	1,817	0.723	1,054	0.831	1.00	-	-
Arg/His, Arg/Ser	1	635	0.253	203	0.160	1.78	1.49 - 2.15	6.79×10^{-10}
His/Ser, His/His, Ser/Ser	2	61	0.024	11	0.009	3.23	1.64 - 6.35	6.95×10^{-4}

OR and *P* values are from logistic regression analysis adjusting for age and sex. Participants with Arg/Arg were used as the reference. CI, confidence interval; OR, odds ratio.

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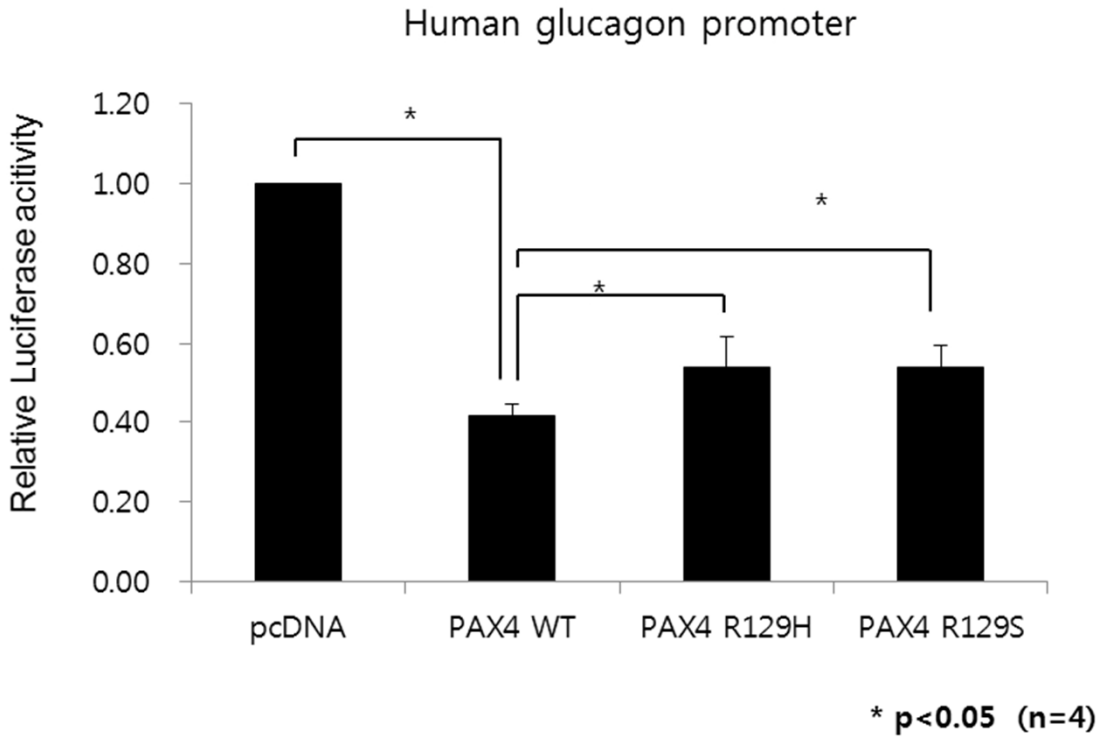
Association of *PAX4* Arg192His variant and metabolic phenotypes in T2D participants

PAX4 Arg192His genotype	Arg/Arg	Arg/His	His/His	β (95% CI)	*P*
N	1,943	436	21		
Age at diagnosis (years)	**47.7 ± 11.7**	**46.3 ± 11.5**	**40.7 ± 9.7**	**-1.69 (-2.46 - -0.93)**	***1.55×10^{-10}***
BMI (kg/m^2)	24.4 ± 3.19	24.3 ± 3.0	24.6 ± 3.8	-0.05 (-0.29 - 0.30)	0.972
Waist circumference (cm)	91.0 ± 9.6	90.4 ± 9.3	91.5 ± 9.2	-0.42 (-1.36 - 0.51)	0.377
SBP (mmHg)	129 ± 18	129 ± 18	130 ± 16	0.60 (-1.10 - 2.30)	0.489
Fasting glucose (mg/dl)	147.3 ± 51.3	147.8 ± 48.9	173.5 ± 56.5	2.80 (-1.98 - 7.56)	0.251
HbA1c (%)	7.77 ± 1.61	7.90 ± 1.70	8.06 ± 2.11	0.13 (-0.03 - 0.28)	0.107
C-peptide (ng/ml)	**2.22 ± 1.50**	**2.06 ± 1.43**	**1.26 ± 0.55**	**-0.20 (-0.38 - -0.03)**	***0.024***
Total cholesterol (mg/dl)	181 ± 40	186 ± 42	189 ± 32	4.37 (0.53 - 8.21)	***0.026***
Triacylglyceride (mg/dl)	151 ± 104	159 ± 108	132 ± 90	4.80 (-0.54 - 15.00)	0.356
HDL cholesterol (mg/dl)	48 ± 14	48 ± 13	53 ± 14	0.24 (-1.07 - 1.55)	0.718
LDL cholesterol (mg/dl)	115 ± 36	117 ± 41	115 ± 23	2.01 (-1.73 - 5.75)	0.292
MDRD eGFR (ml/min/1.73m^2)	71 ± 31	68 ± 29	56 ± 27	-3.94 (-7.09 - -0.79)	***0.014***

Kwak SH et al., Diabetes Sep 2018

Effect of PAX4 variants on glucagon promoter suppression



The α-TC1.9 cells were co-transfected with either 150 ng pcDNA-*PAX4* (192Arg) or pcDNA-PAX4 (192His or 192Ser) together with 300 ng pGL3-human glucagon promoter and 50 ng RSV β-galactosidase. Luciferase activity was measured after 48 hours of transfection. Wild type *PAX4* could suppress glucagon expression by 58%. However, both Arg192His and Arg192Ser variants showed an impaired ability to suppress glucagon compared to wild type ($P < 0.05$).

CONTENTS

Validation of Nonsynonymous Variants of T2D

Chr	Position (hg19)	Alleles (Ref, Alt)	Gene	HGVS (rsID)	Korean AF	European AF	Study	OR 95% CI	*P*	AF Case	AF Control
7	127,253,550	C, T	***PAX4***	**p.Arg192His (rs2233580)**	0.086	0.000	Stage 1. WES	2.62 (1.64 - 4.18)	1.73×10^{-5}	0.122	0.057
							Stage 2. Exome Chip	1.67 (1.33 - 2.08)	3.16×10^{-6}	0.094	0.059
							Stage 3. Replication	1.40 (1.26 - 1.56)	9.22×10^{-10}	-	-
							Meta-Analysis	**1.48 (1.35 - 1.63)**	**4.47×10^{-16}**	-	-
6	39,033,595	G, A	***GLP1R***	**p.Arg131Gln (rs3765467)**	0.211	0.001	Stage 1. WES	0.74 (0.55 - 0.98)	0.036	0.196	0.258
							Stage 2. Exome Chip	0.78 (0.69 - 0.90)	3.60×10^{-4}	0.198	0.234
							Stage 3. Replication	0.87 (0.81 - 0.93)	5.77×10^{-5}	-	-
							Meta-Analysis	**0.84 (0.80 - 0.90)**	**3.55×10^{-8}**	-	-
4	1,349,029	G, A	*UVSSA*	p.Arg391His (rs2276904)	0.376	0.031	Stage 1. WES	0.91 (0.72 - 1.15)	0.441	0.363	0.393
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							Stage 2. Exome Chip	0.63 (0.49 - 0.80)	1.58×10^{-4}	0.046	0.068
							Stage 3. Replication	0.99 (0.86 - 1.13)	0.835	-	-
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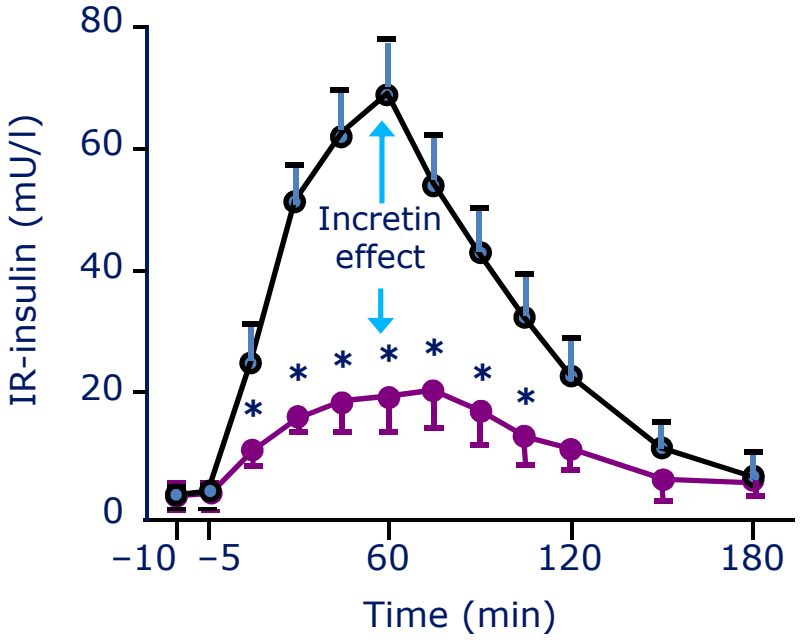
							Meta-Analysis	0.98 (0.92 - 1.05)	0.582		

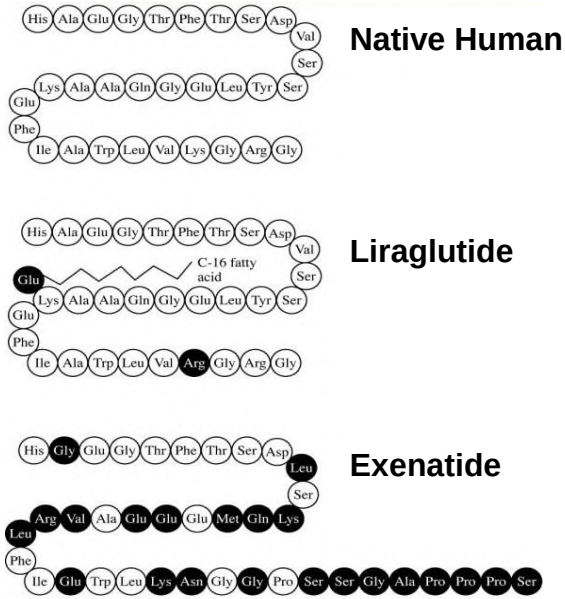
OR and *P* values are from T2D association testing results for alternative alleles adjusted for age, sex, and principle components. Stage 1, 2, and 3 association were analysed with the Firth bias-corrected likelihood ratio test. Meta-analysis was performed using METAL with the inverse variance weighted method under a fixed effects model. Alleles are aligned to the forward strand of the Human Genome Version 19 (hg19). Alt, alternative allele; AF, allele frequency; Chr, chromosome; CI, confidence interval; EUR, Europeans; HGVS, Human Genome Variation Society nomenclature; OR, odds ratio; Ref, reference allele; rsID, dbSNP reference ID. The genome-wide significance threshold was set to $P < 5.0\times10^{-8}$.

Incretin Therapy

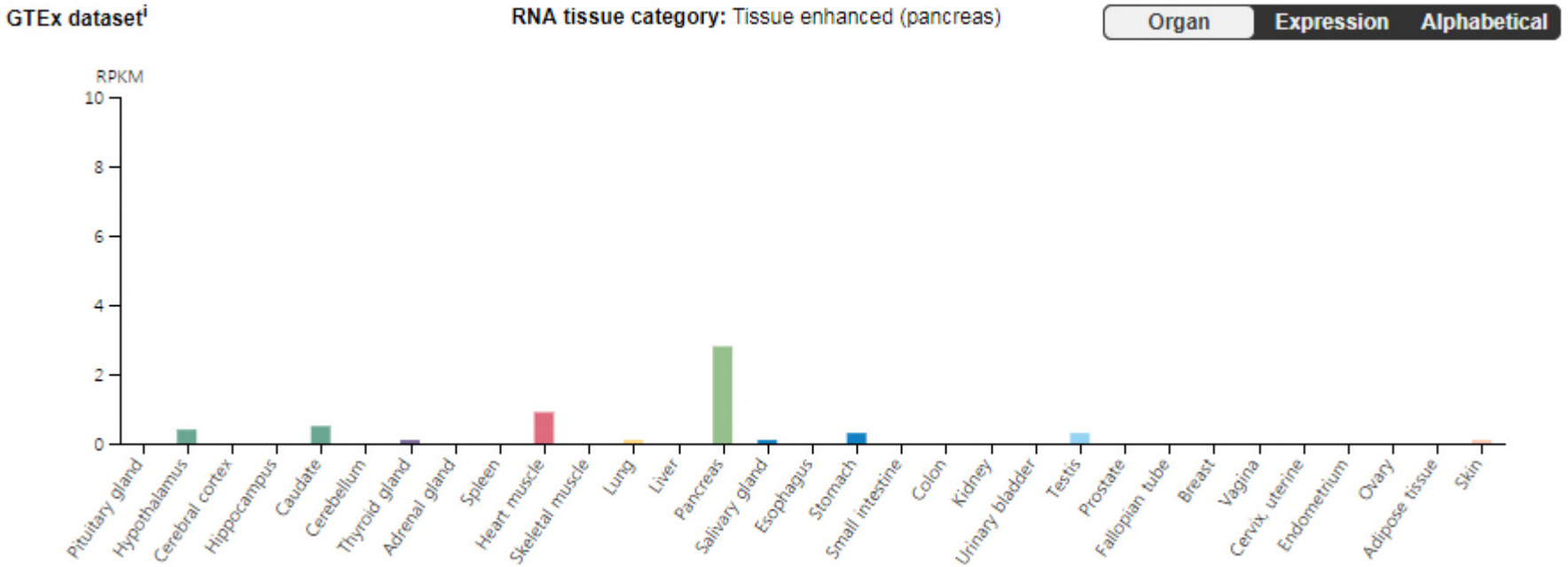
- Glucagon Like Peptide (GLP)-1 Analogues
- DiPeptidylPeptidase (DPP)-4 Inhibitors



Insulin response to oral glucose load (50 g/400 ml, ●) and during isoglycaemic i.v. glucose infusion (●)



GLP-1 Receptor Expression



ARTICLE

doi:10.1038/nature22800

Crystal structure of the GLP-1 receptor bound to a peptide agonist

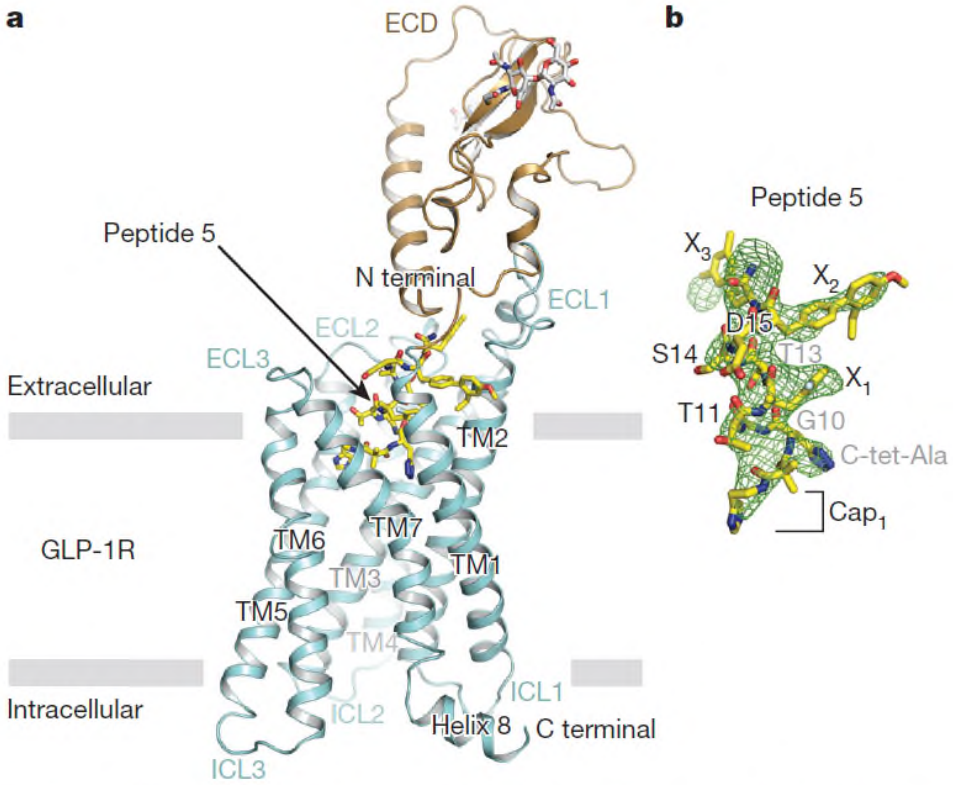
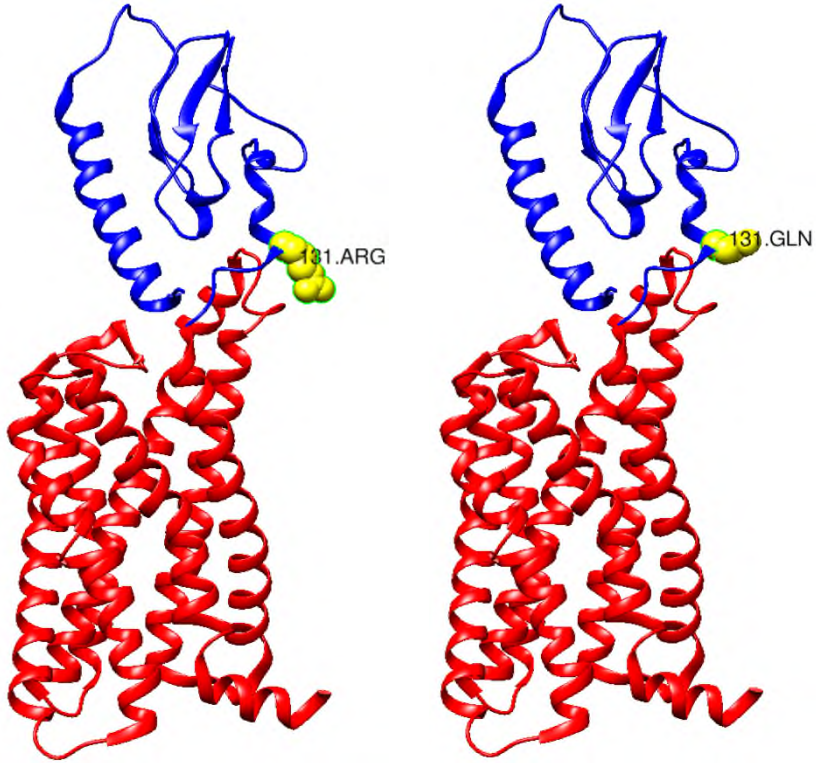


Figure 1 | The overall structure of GLP-1R in complex with peptide 5. **a**, Ribbon representation of GLP-1R (TMD coloured cyan; ECD coloured brown), as viewed parallel to the membrane with approximate membrane boundaries indicated by grey boxes. The glycosylation modification resolved on the receptor ECD is shown in stick representation with carbon, nitrogen and oxygen atoms coloured grey, blue and red, respectively. **b**,The peptide 5 agonist is shown in stick representation with carbon, nitrogen and oxygen atoms coloured yellow, blue and red, respectively, $F_o - F_c$ omit density map for peptide 5 is contoured at 2.5σ.

GLP1R 131 Arg **GLP1R 131 Gln**



Characteristics	Arginine	Glutamine
Polarity	Positively Charged	Polar Uncharged
pH	Basic	Neutral
Residue weight	156	128
Secondary structure propensity	α indifferent β indifferent	α former β former

Association of nonsynonymous variants with glycemic traits in non-diabetic controls (N = 7,516)

Gene	HGVS (rsID)	Fasting Glucose		1-hour Glucose		2-hour Glucose		Fasting Insulin		HbA1c	
		β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
PAX4	p.Arg192His (rs2233580)	0.103 (0.036 - 0.170)	**2.68×10^{-3}**	0.071 (0.004 - 0.138)	**0.038**	-0.038 (-0.105 - 0.029)	0.263	0.039 (-0.028 - 0.106)	0.258	0.029 (-0.038 - 0.096)	0.402
GLP1R	p.Arg131Gln (rs3765467)	-0.075 (-0.114 - -0.035)	**2.00×10^{-4}**	-0.048 (-0.088 - -0.009)	**0.016**	-0.052 (-0.091 - -0.012)	**0.010**	-0.031 (-0.071 - 0.008)	0.120	-0.053 (-0.093 - -0.014)	**8.52×10^{-3}**
UVSSA	p.Arg391His (rs2276904)	-0.001 (-0.033 - 0.032)	0.956	-0.024 (-0.056 - 0.009)	0.154	0.009 (-0.023 - 0.042)	0.575	-0.018 (-0.051 - 0.014)	0.274	-0.016 (-0.048 - 0.017)	0.349
JMJD1	p.Ser464Thr (rs10761725)	0.014 (-0.019 - 0.046)	0.415	0.059 (0.026 - 0.091)	**3.90×10^{-4}**	0.047 (0.014 - 0.079)	4.62×10^{-3}	-0.020 (-0.053 - 0.012)	0.220	-0.005 (-0.037 - 0.028)	0.783

β and *P* values are from linear regression analysis for alternative alleles adjusted for age, and sex using additive genetic model. Variables were inverse normal transformed before analysis. HGVS, Human Genome Variation Society nomenclature; rsID, dbSNP reference ID.

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Observational Study

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A genetic variant in *GLP1R* is associated with response to DPP-4 inhibitors in patients with type 2 diabetes

Eugene Han, MD[a,b], Hye Sun Park, MD[a], Obin Kwon, MD, PhD[c], Eun Yeong Choe, MD[b], Hye Jin Wang, PhD[d], Yong-ho Lee, MD, PhD[a,b], Sang-Hak Lee, MD, PhD[b,e], Chul Hoon Kim, MD, PhD[f], Lee-Kyung Kim, MD[g], Soo Heon Kwak, MD, PhD[g], Kyong Soo Park, MD, PhD[g], Chul Sik Kim, MD, PhD[h,*], Eun Seok Kang, MD, PhD[a,b,*]

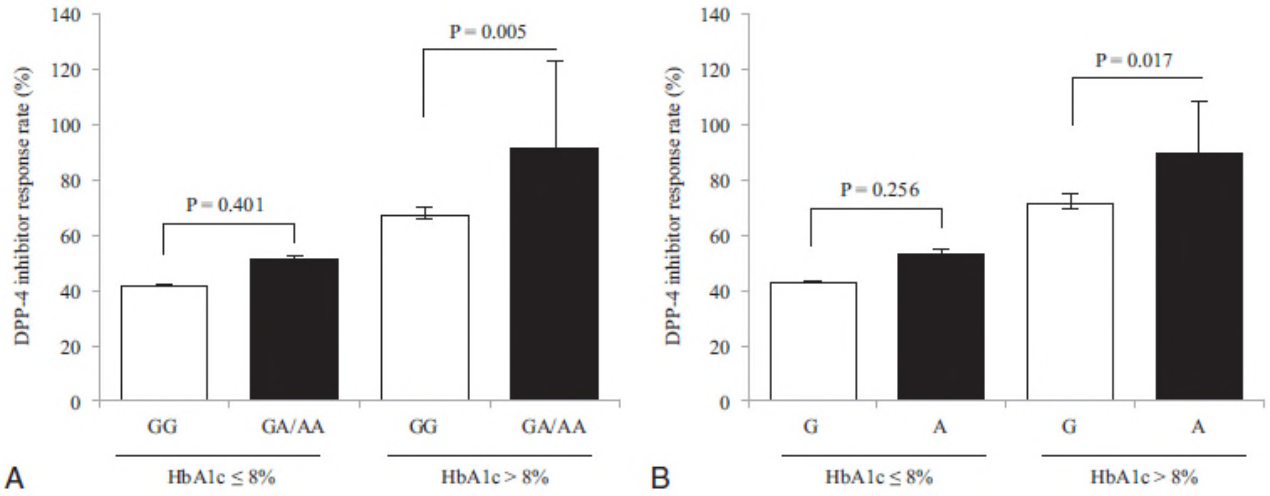


Figure 1. Differences in the response rates to DPP-4 inhibitors according to baseline HbA1c and rs3765467. (A) The proportion of responders according to HbA1c and rs3765467 genotype, (B) the proportion of responders according to HbA1c and rs3765467 allele. Error bars represent 95% confidence intervals. DPP-4 = dipepdityl peptidase-4, HbA1c = glycated hemoglobin.

Association of nonsynonymous variants with cardiovascular disease (N = 1,496)

Gene	HGVS (rsID)	CVD Cases	CVD Controls	CVD Cases AF	CVD Controls AF	OR (95% CI)	*P*
PAX4	p.Arg192His (rs2233580)	239	1257	0.125	0.096	1.30 (0.95 - 1.78)	0.100
GLP1R	p.Arg131Gln (rs3765467)	239	1257	0.159	0.199	**0.77 (0.59 - 0.99)**	**0.041**
UVSSA	p.Arg39His (rs2276904)	239	1257	0.370	0.378	0.97 (0.79 - 1.18)	0.748
JMJD1	p.Ser464Thr (rs10761725)	239	1257	0.417	0.445	0.83 (0.68 - 1.02)	0.077

OR and P values are from CVD association testing results for alternative alleles adjusted for age, and sex. A subset of T2D patient (N = 1,496) who's CVD event status was available from stage 1, and 2 analyses was investigated with logistic regression. CVD events included stable or unstable angina, myocardial infarction, history of percutaneous coronary intervention, coronary artery bypass surgery, ischemic or haemorrhage stroke. AF, allele frequency; CVD, cardiovascular disease; HGVS, Human Genome Variation Society nomenclature; rsID, dbSNP reference ID.

Kwak SH et al., Diabetes Sep 2018

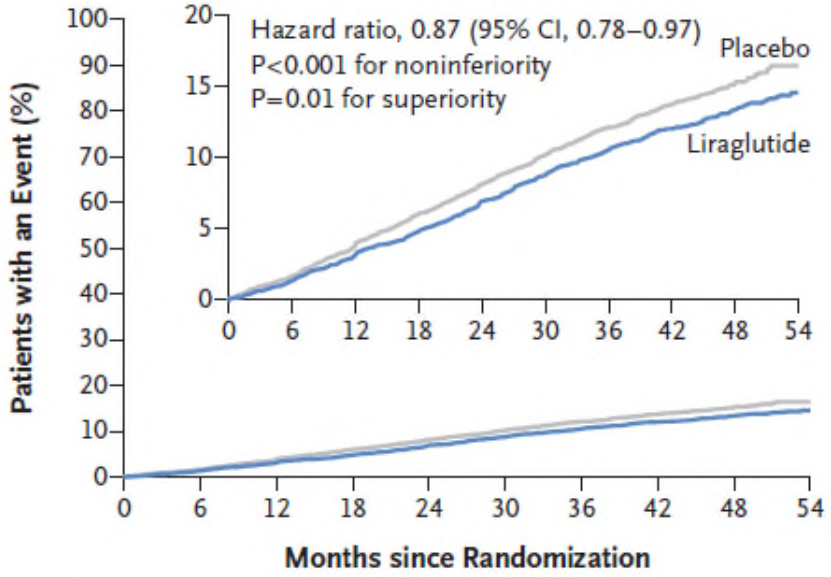
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

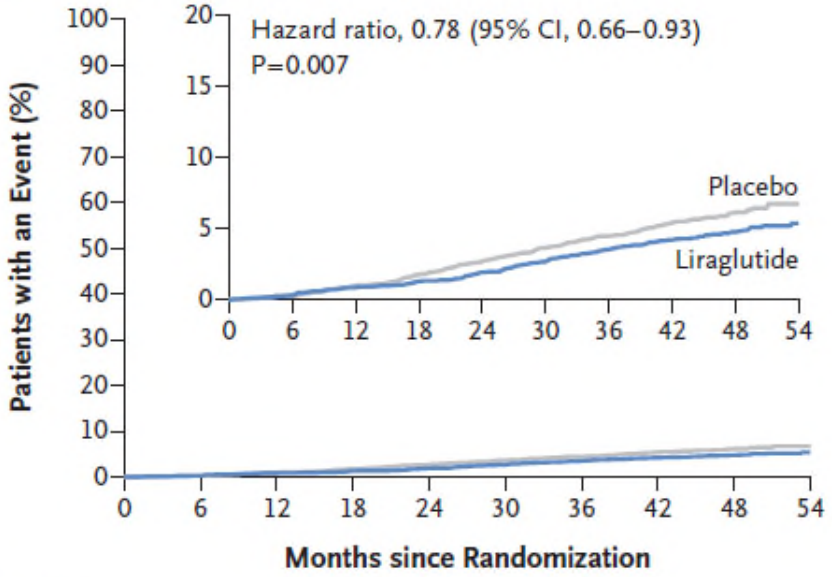
Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

A Primary Outcome



No. at Risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

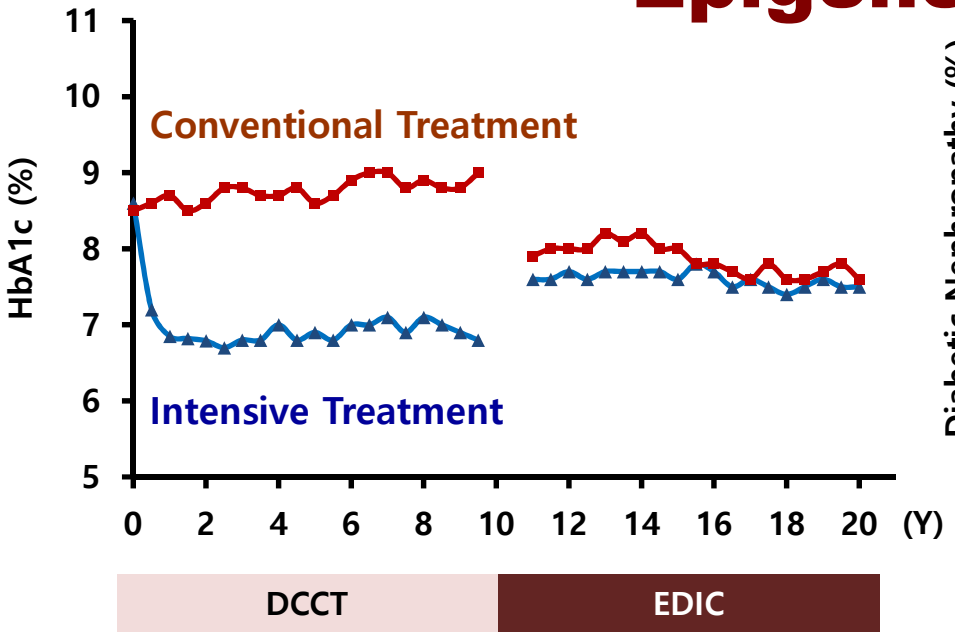
B Death from Cardiovascular Causes

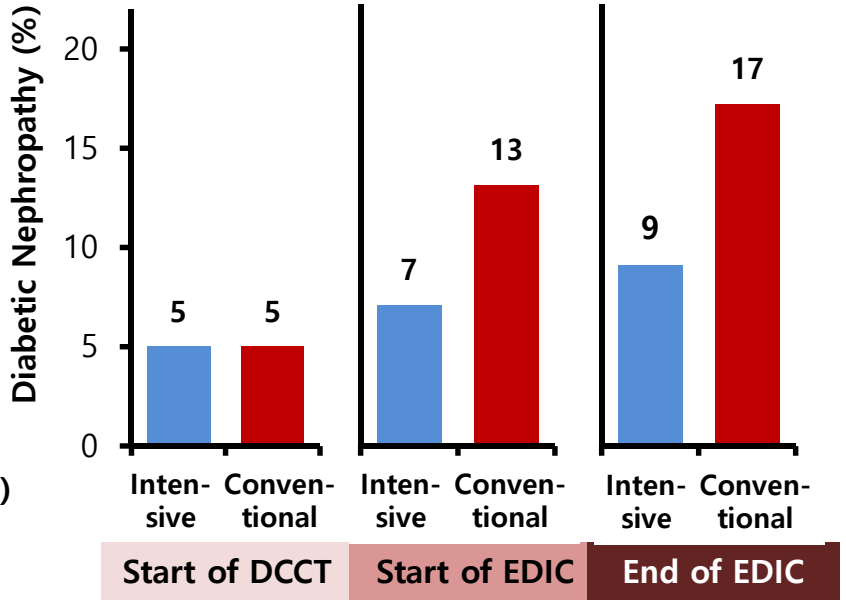


No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

CONTENTS

Microvascular Complications and Epigenetics

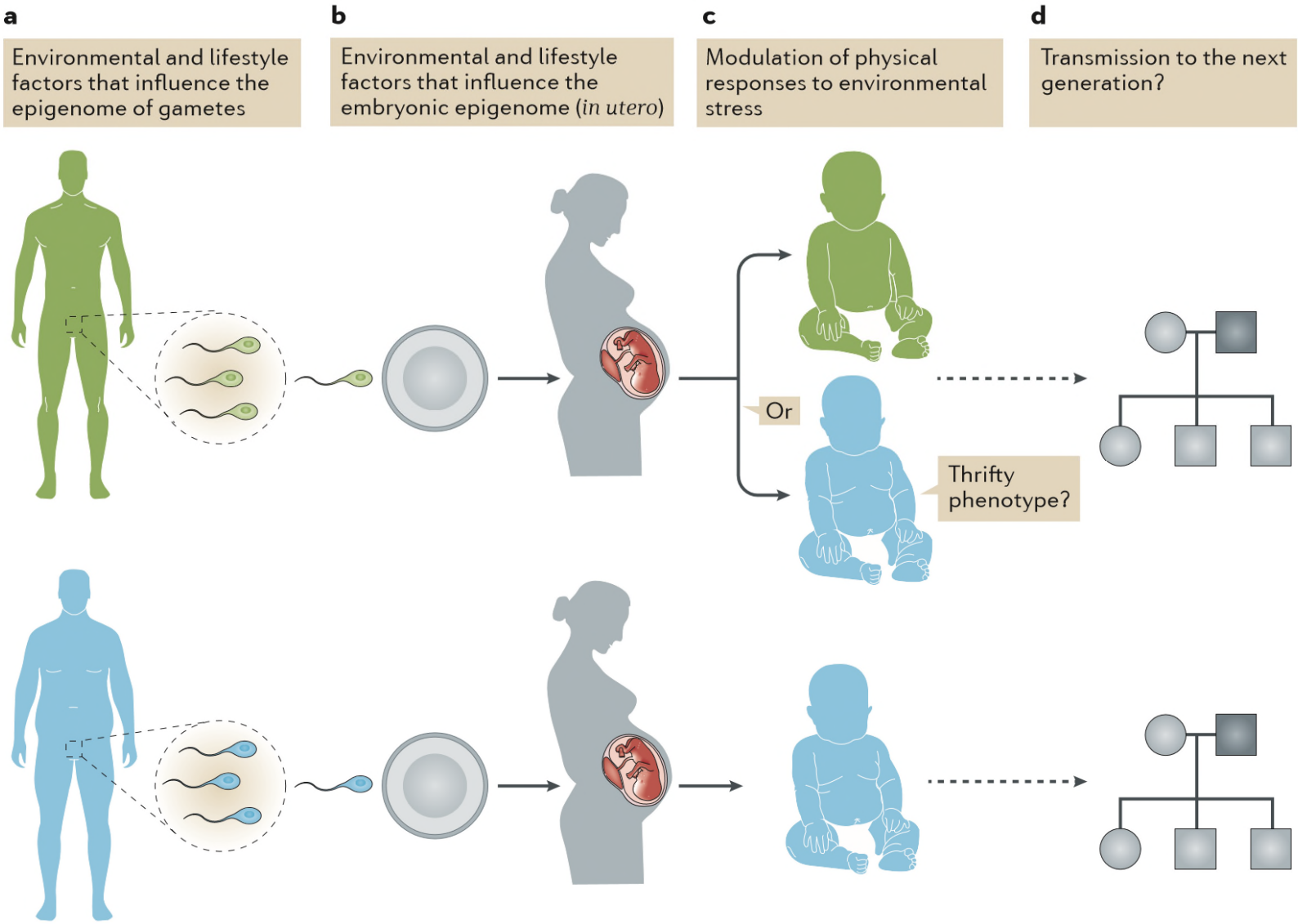




EDIC Study

- **Legacy Effect (Metabolic Memory)**
- Those who had poor glycemic control during the early stage of diabetes have higher incidence of diabetic microvascular complications even after intensive glycemic control during later 10 years of diagnosis
- It is plausible that **epigenetic change ensued by hyperglycemia** could be the cause of these metabolic memory

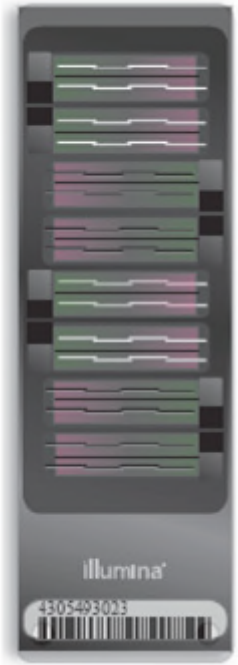
Intrauterine Environment (DoHAD)

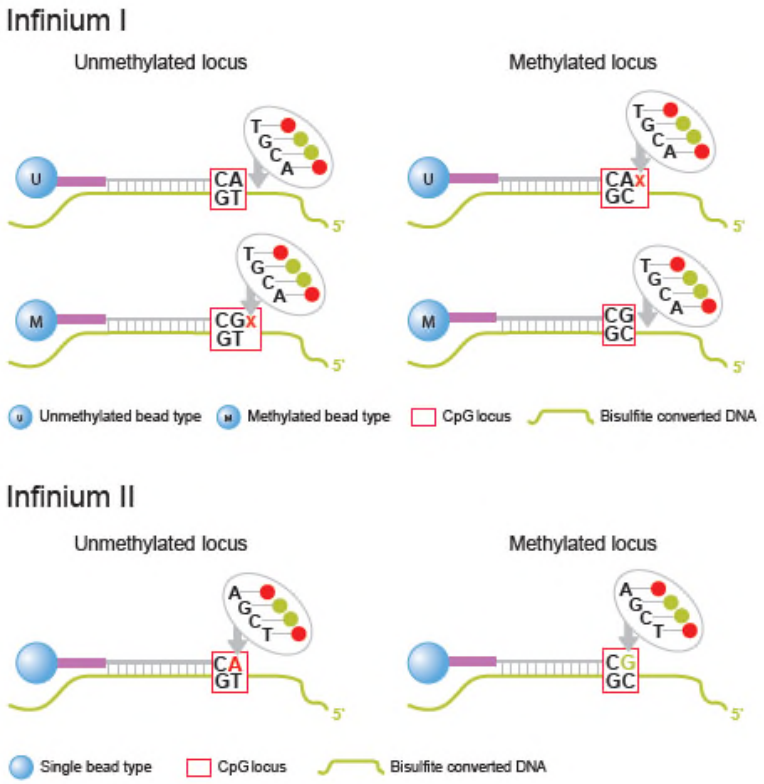


Barres R and Zierath JR, Nat Rev Endo 2017

Infinium® MethylationEPIC BeadChip

Affordable methylome analysis meets cutting edge content.





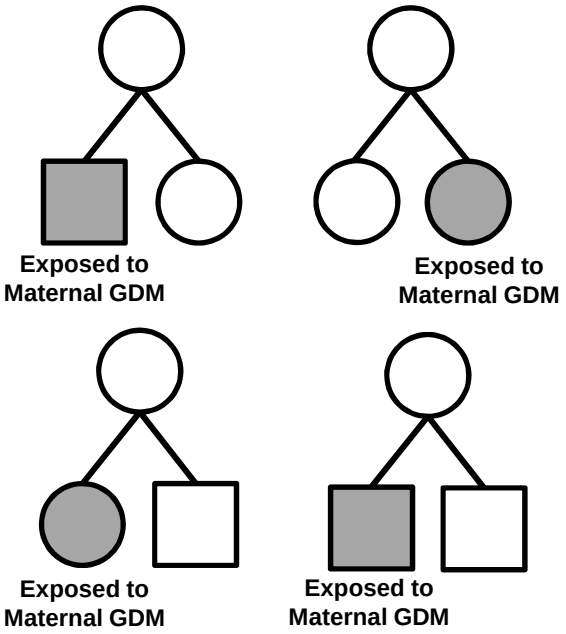
Unique Combination of Coding Region and Enhancer-Wide Coverage, High-Throughput, and Low Cost

Over 850,000 methylation sites per sample at single-nucleotide resolution

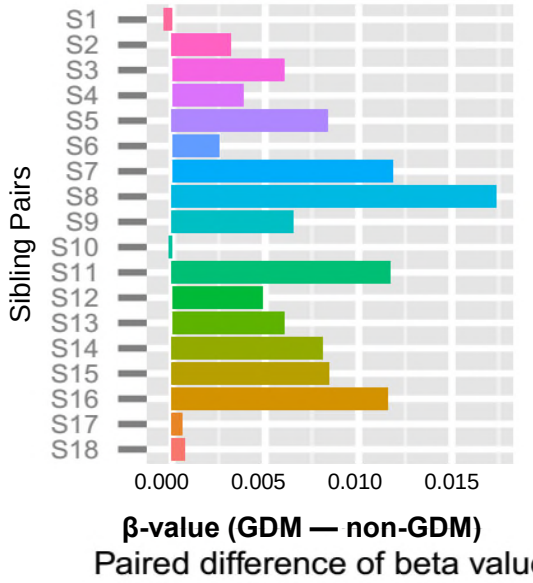
Figure 4: Broader Coverage Using Infinium I and II Assay Designs—The MethylationEPIC BeadChip employs both Infinium I and Infinium II assays. Infinium I assay design employs 2 bead types per CpG locus, 1 each for the methylated and unmethylated states. The Infinium II design uses 1 bead type, with the methylated state determined at the single base extension step after hybridization.

Intrauterine Exposure to Maternal Hyperglycemia and DNA Methylation Change

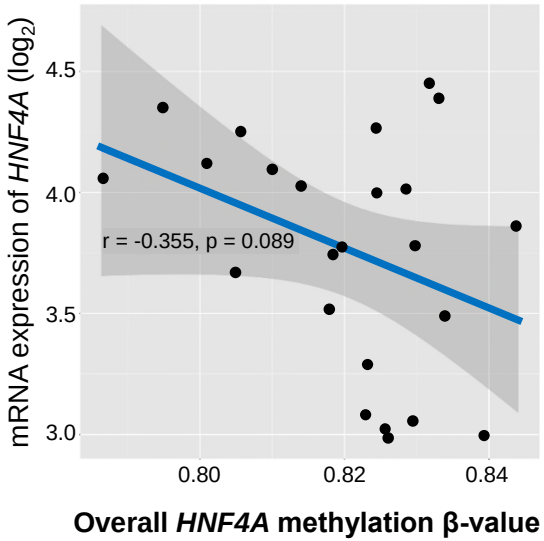
18 Sibling Pairs Discordant for Exposure to Intrauterine Hyperglycemia



- ***HNF4A* site (cg08407434) / region specific analysis**



Most of the GDM-exposed siblings had higher level of methylation at cg08407434 compared to their control siblings (adjusted for age, sex and cell composition).



DNA methylation at *HNF4A* was associated with decreasing trend of *HNF4A* mRNA expression.

Kim EA and Kwak SH et al, Epigenetics 2017

Epigenome-wide association of DNA methylation markers in peripheral blood from Indian Asians and Europeans with incident type 2 diabetes: a nested case-control study

John C Chambers*, Marie Loh*, Benjamin Lehne*, Alexander Drong*, Jennifer Kriebel*, Valeria Motta*, Simone Wahl, Hannah R Elliott, Federica Rota, William R Scott, Weihua Zhang, Sian-Tsung Tan, Gianluca Campanella, Marc Chadeau-Hyam, Loic Yengo, Rebecca C Richmond, Martyna Adamowicz-Brice, Uzma Afzal, Kiymet Bozaoglu, Zuan Yu Mok, Hong Kiat Ng, François Pattou, Holger Prokisch, Michelle Ann Razario, Letizia Tarantini, James Abbott, Mika Ala-Korpela, Benedetta Albetti, Ole Ammerpohl, Pier Alberto Bertazzi, Christine Blancher, Robert Caiazzo, John Danesh, Tom R Gaunt, Simon de Lusignan, Christian Gieger, Thomas Illig, Sujeet Jha, Simon Jones, Jeremy Jowett, Antti J Kangas, Anuradhani Kasturiratne, Norihiro Kato, Navaratnam Kotea, Sudhir Kowlessur, Janne Pitkaniemi, Prakash Punjabi, Danish Saleheen, Clemens Schafmayer, Pasi Soininen, E-Shyong Tai, Barbara Thorand, Jaakko Tuomilehto, Ananda Rajitha Wickremasinghe, Soterios A Kyrtopoulos, Timothy J Aitman, Christian Herder, Jochen Hampe, Stéphane Cauchi, Caroline L Relton, Philippe Froguel, Richie Soong, Paolo Vineis, Marjo-Riitta Jarvelin*, James Scott*, Harald Grallert*, Valentina Bollati*, Paul Elliott*, Mark I McCarthy*, Jaspal S Kooner*

	Chromosome	Position	Locus	Discovery		Replication		Combined		$P_{heterogeneity}$†
				RR (95%CI)*	p value	RR (95%CI)*	p value	RR (95%CI)*	p value	
cg19693031	1	145 441 552	*TXNIP*	0·92 (0·91–0·94)	$1·0 \times 10^{-13}$	0·96 (0·94–0·98)	$2·5 \times 10^{-5}$	0·92 (0·90–0·94)	$1·5 \times 10^{-18}$	0·98
cg09152259	2	128 156 114	*PROC*	0·95 (0·93–0·97)	$9·3 \times 10^{-8}$	0·99 (0·97–1·01)	0·32	0·95 (0·93–0·97)	$4·8 \times 10^{-7}$	0·04
cg04999691	7	150 027 050	*C7orf29*	0·95 (0·93–0·96)	$1·4 \times 10^{-8}$	1·00 (0·98–1·02)	0·71	0·96 (0·94–0·98)	$4·8 \times 10^{-6}$	0·004
cg11024682	17	17 730 094	*SREBF1*	1·06 (1·04–1·08)	$8·4 \times 10^{-8}$	1·03 (1·01–1·05)	0·0054	1·07 (1·04–1·09)	$3·0 \times 10^{-10}$	0·07
cg02650017	17	47 301 614	*PHOSPHO1*	0·94 (0·92–0·96)	$2·1 \times 10^{-8}$	0·97 (0·95–0·99)	0·0012	0·94 (0·92–0·95)	$4·1 \times 10^{-12}$	0·48
cg18181703	17	76 354 621	*SOCS3*	0·95 (0·93–0·97)	$2·1 \times 10^{-7}$	0·97 (0·95–0·99)	0·0016	0·94 (0·92–0·96)	$4·7 \times 10^{-10}$	0·76
cg06500161	21	43 656 587	*ABCG1*	1·08 (1·06–1·10)	$2·2 \times 10^{-13}$	1·04 (1·02–1·06)	0·00012	1·09 (1·07–1·11)	$1·1 \times 10^{-17}$	0·32

RR=relative risk. *Associated with a 1% increase in respective methylation marker in the discovery phase (1074 Indian Asians with incident type 2 diabetes and 1590 controls), in replication testing among 1141 Europeans (377 with incident type 2 diabetes) and in combined analysis. †Heterogeneity of effect between discovery and replication.

Table 3: **Association of methylation markers with future type 2 diabetes incidence**

TXNIP gene encodes a thioredoxin-binding protein that is a member of the alpha arrestin protein family. This protein results in the accumulation of reactive oxygen species and cellular stress. Elevated TXNIP levels induce β-cell apoptosis, whereas TXNIP deficiency protects against type 1 and type 2 diabetes by promoting β-cell survival.

Epigenome-wide association of DNA methylation markers in peripheral blood from Indian Asians and Europeans with incident type 2 diabetes: a nested case-control study

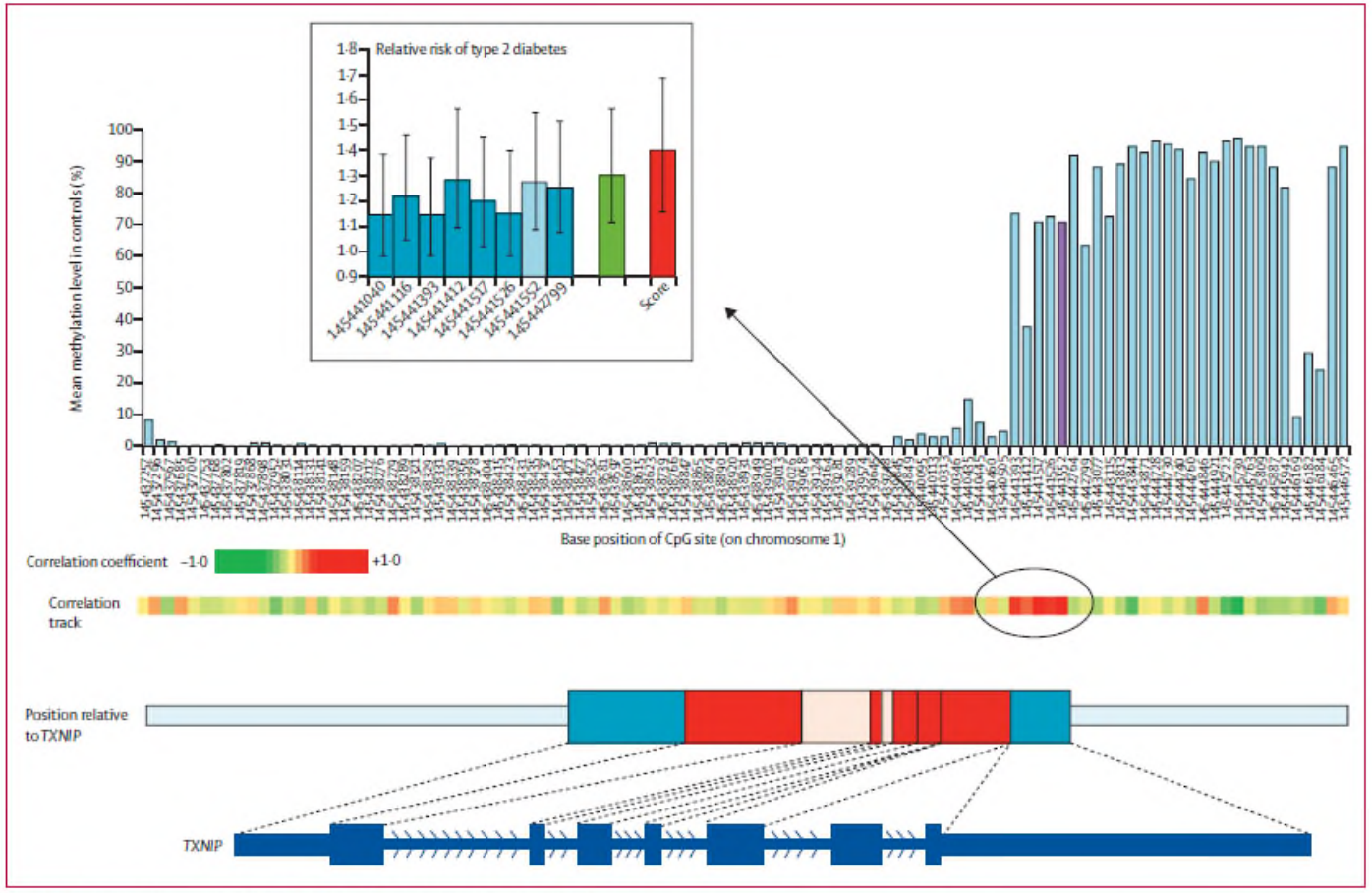
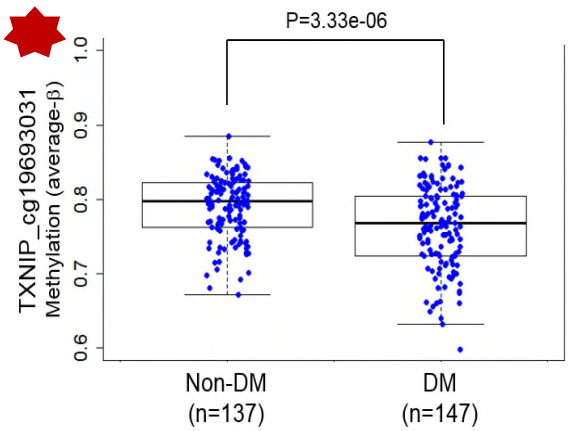
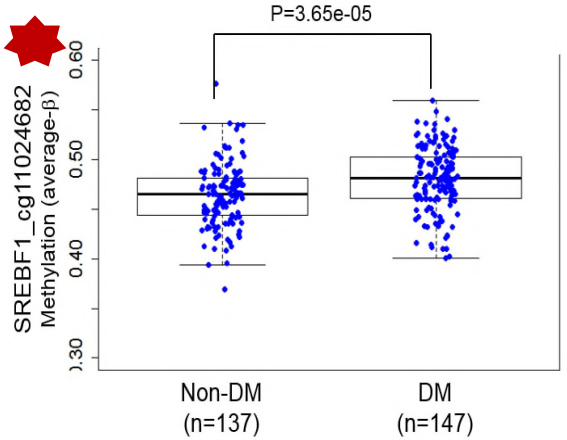
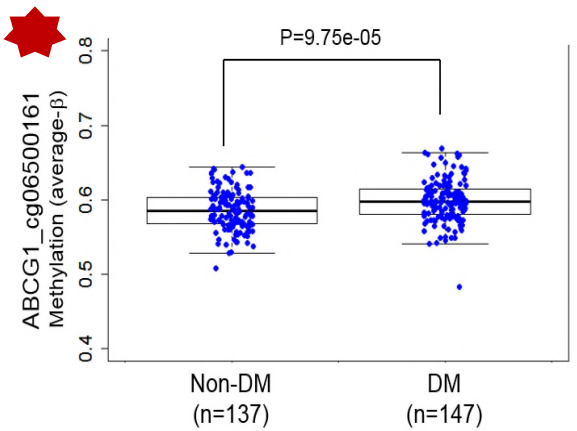


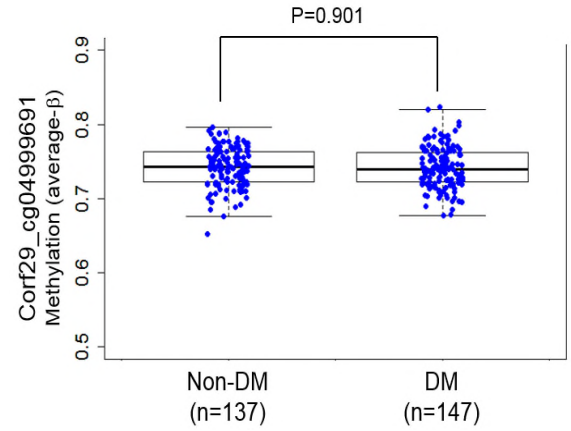
Figure 3: **Targeted resequencing of the *TXNIP* locus by next-generation sequencing**
Bars show mean methylation at the CpG sites assessed. The purple bar is the sentinel marker, as identified by epigenome-wide association analyses. The correlation track shows the correlation between methylation at each CpG site with the sentinel marker. The inset graph shows the relative risk for type 2 diabetes associated with a 1 SD reduction in methylation or methylation score for the methylation markers at the *TXNIP* locus identified by targeted resequencing. Results are shown for the eight individual CpG sites assayed by pyrosequencing (blue; light blue for the sentinel marker); the sentinel marker by microarray (green); and the sum of all eight methylation markers (orange). CpG=cytosine-guanine nucleotide pair.

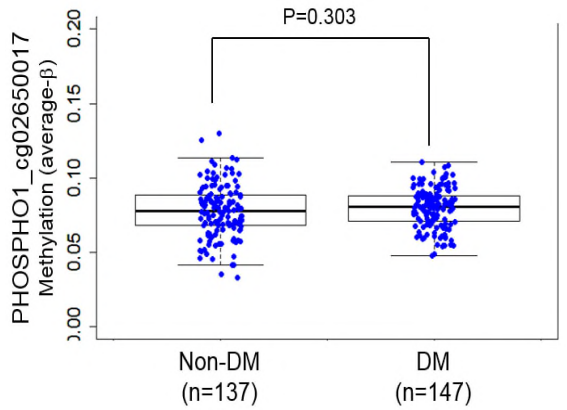
Validation of DNA Methylation Markers in Koreans

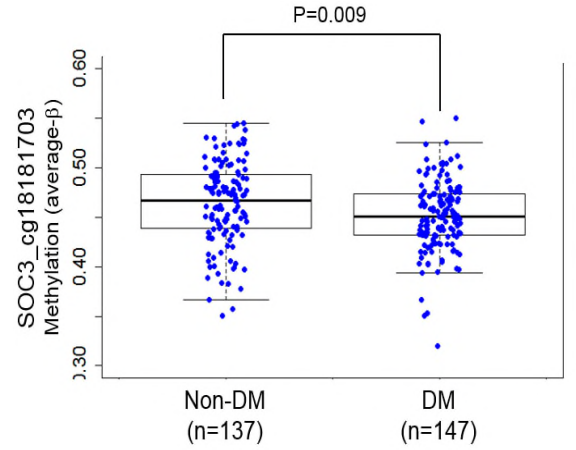






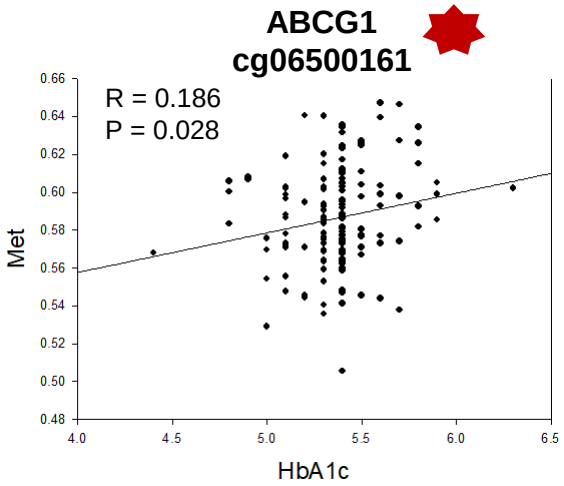


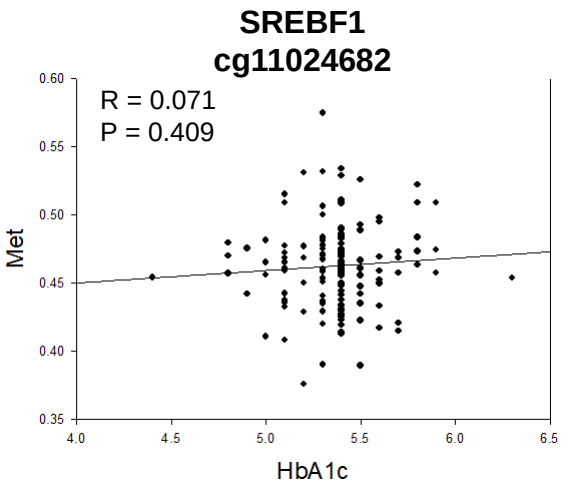


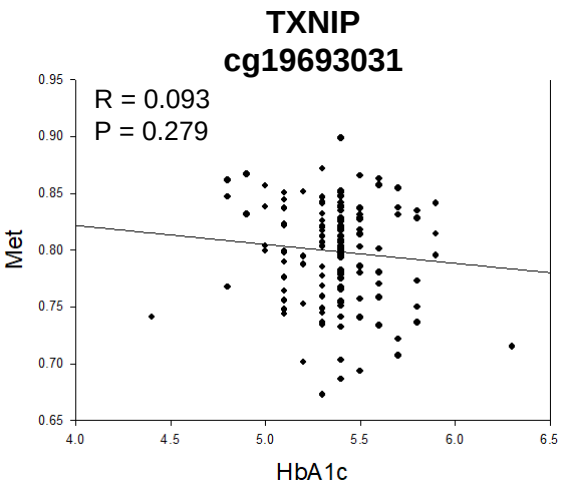


DNA Methylation and Degree of Hyperglycemia

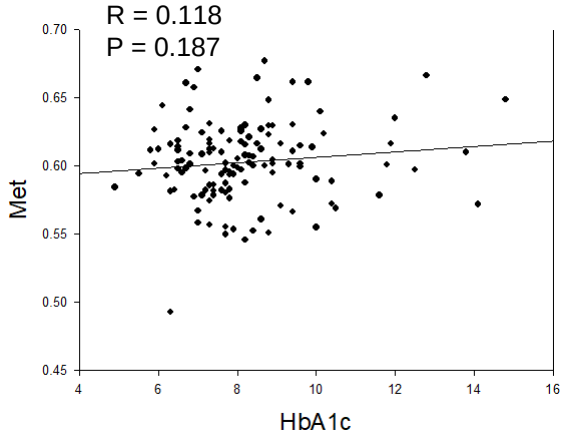
Non-Diabetic Group

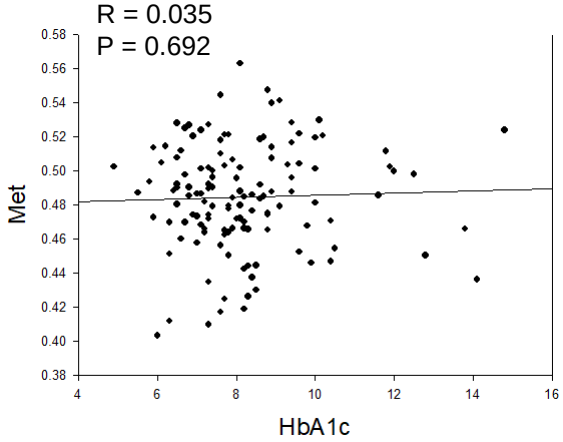


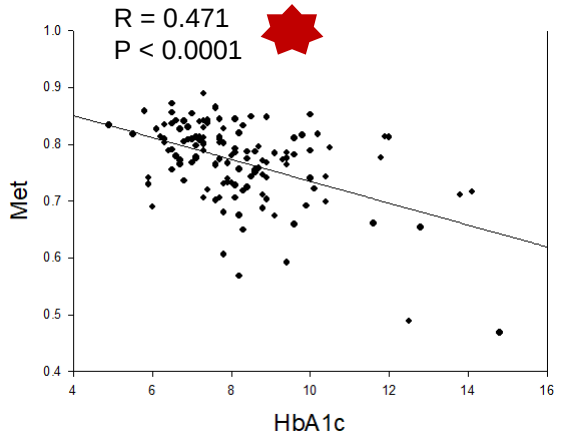




T2D Group







SUMMARY

- There are ethnic as well as individual heterogeneity in the clinical characteristics of type 2 diabetes
- There are population specific variants that could explain ethnic differences of type 2 diabetes
- Amino acid variation in *PAX4* 192 codon (p.R192H, pR192S) is an important risk factor for diabetes in Koreans
- *GLP1R* R131Q is a protective variant of type 2 diabetes which is associated with decreased fasting glucose, decreased HbA1c, and lower risk of cardiovascular disease in Koreans
- There are ongoing efforts to identify epigenetic markers that are associated with progression to diabetes

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Thank You Very Much
For Your Attention.