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Genome-wide association study in a Chinese population identifies a novel locus for T2DM

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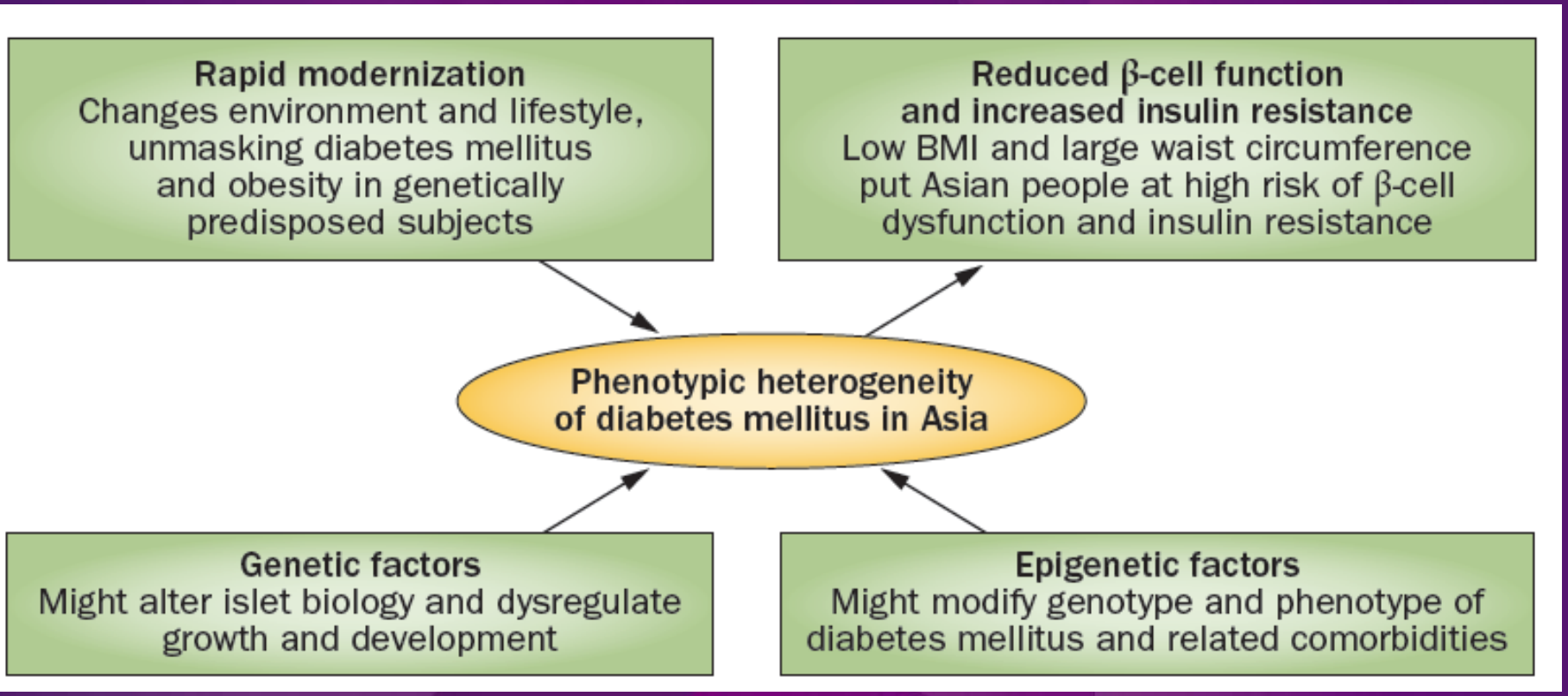
International Diabetes Federation
IDF Centre of Education
2011 - 2015

Outline

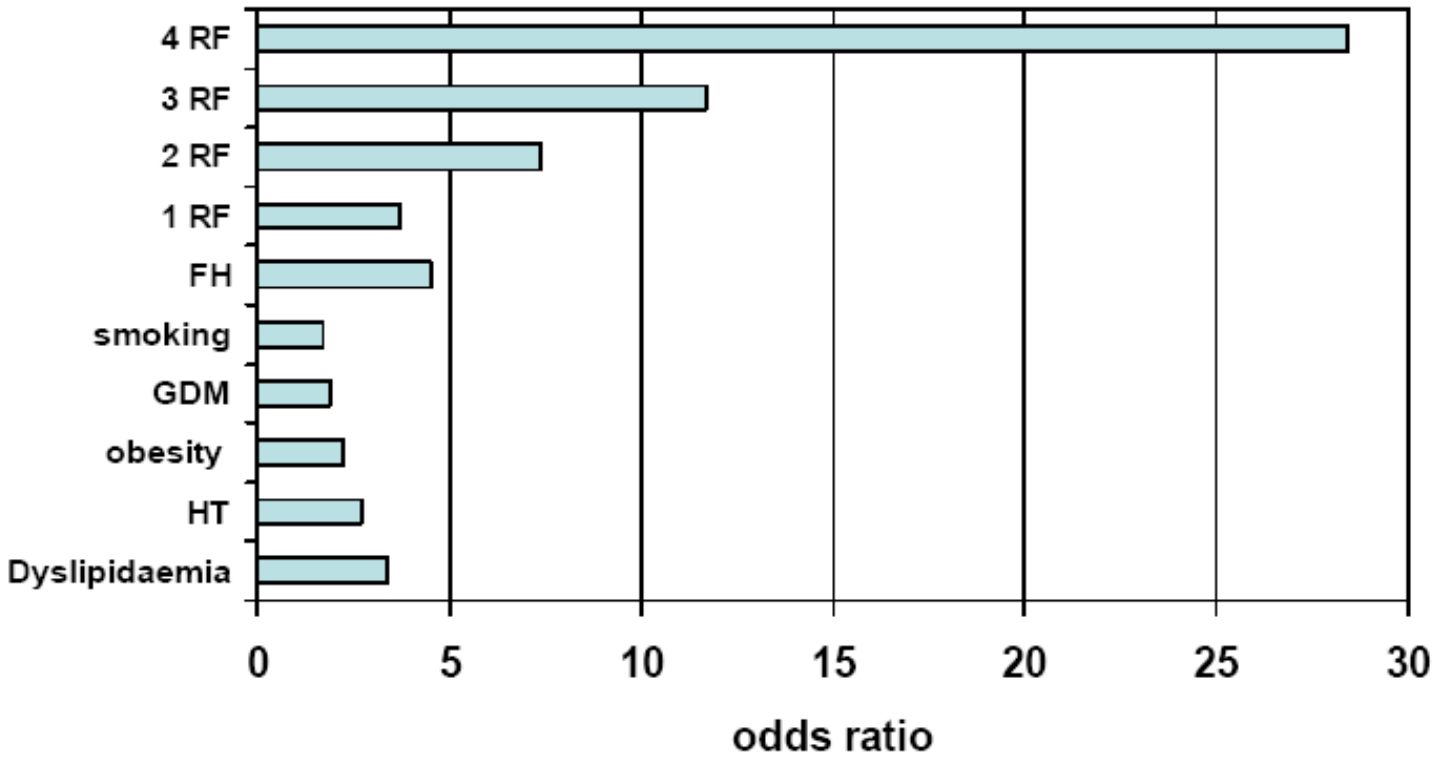
- Update on the genetic basis of T2 DM
- Studies in East Asian populations
- HK-Shanghai GWAS for T2 DM
- Implications of findings and further work

Phenotypic heterogeneity of Diabetes in Asians



Kong AP, et al, Nat Rev Endocrinol 2013; May 28
Ma RC and Chan JC. Ann N Y Acad Sci 2013; April
Ramachandran A, Ma RC et al, Lancet 2010; 375: 408-18
Chan JC et al, JAMA 2009; May 27

Clinical Predictors of T2 DM in Chinese



1649 adults with RF for DM
All underwent 75g OGTT, 15% T2 DM

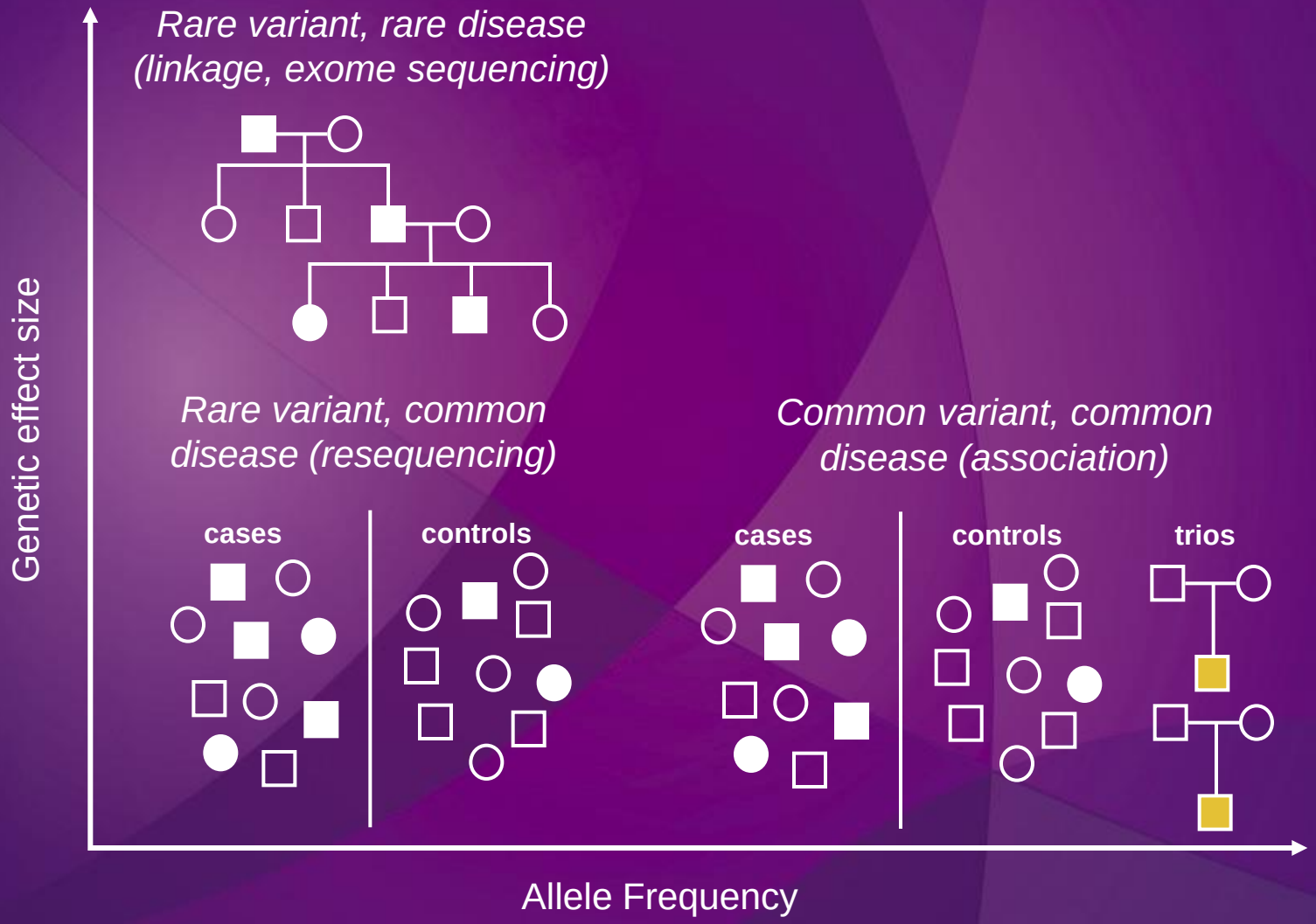
Ko GT et al, Diabetes Care 2002

Searching for disease-related genetic variants

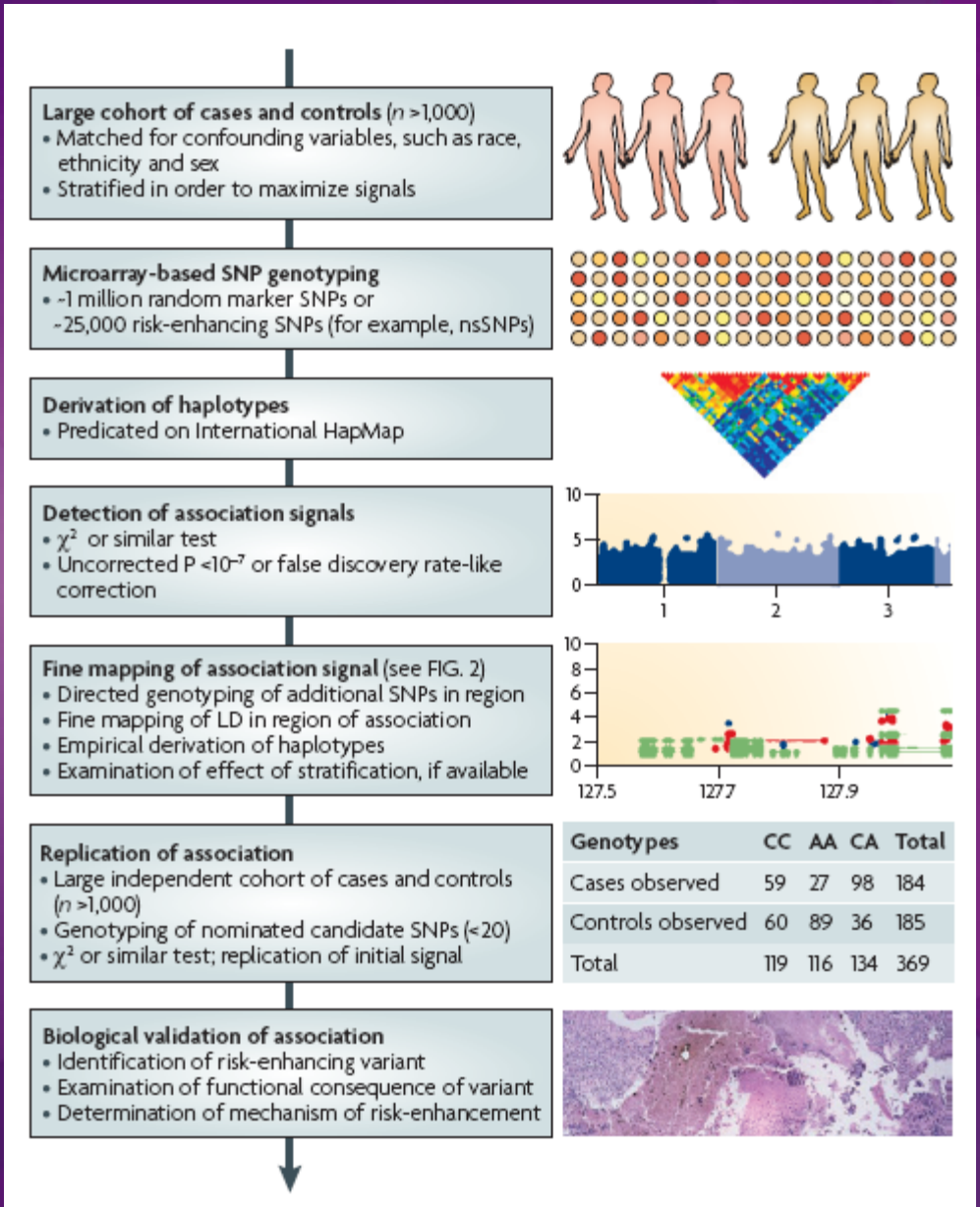
Approaches to genetic studies

- 1) Linkage analysis
- 2) Candidate Gene Approach
  - Case: Control Study
  - Prospective cohort study
- 3) Genome Wide Association Studies
- 4) Bioinformatics analysis

Strategies for discovering genetic factors for diseases

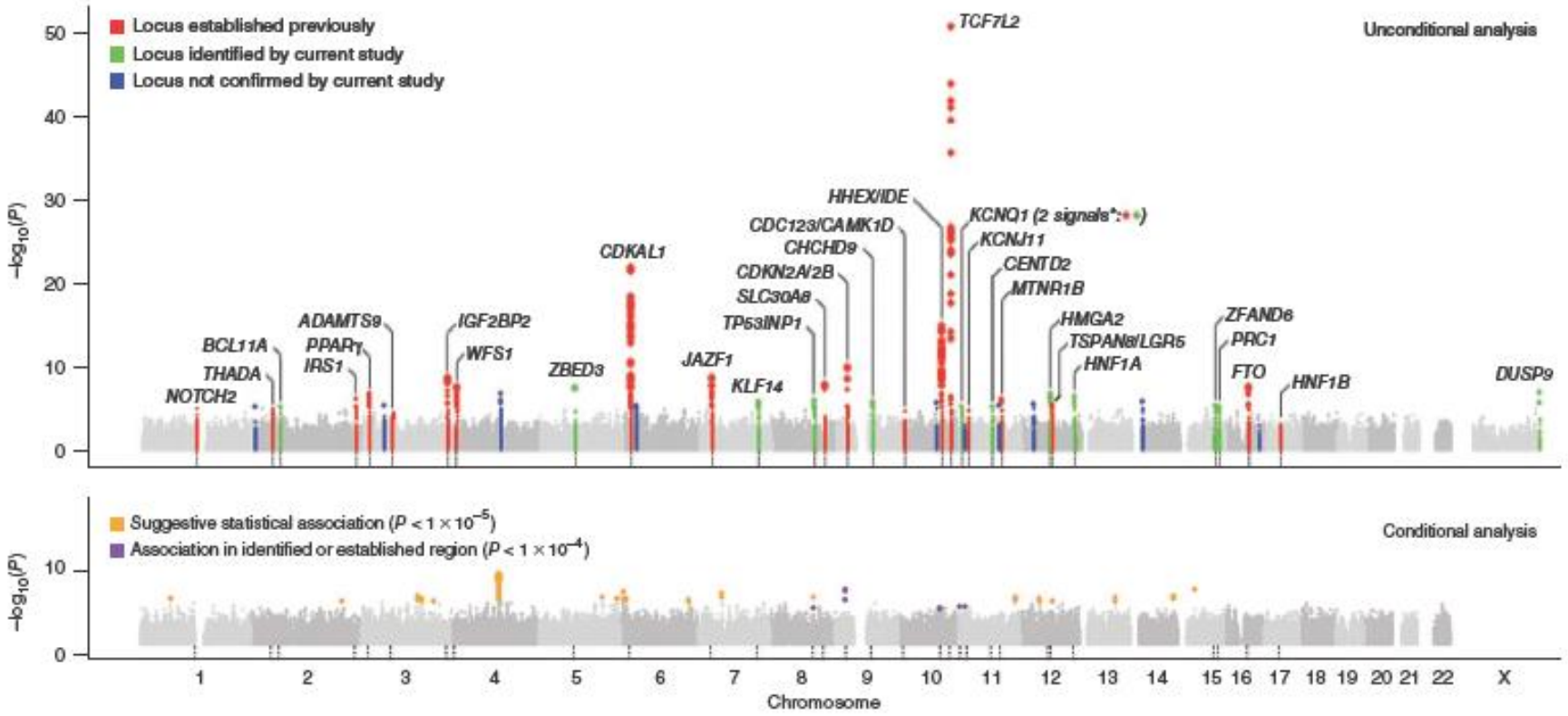


Genome Wide Association Studies (GWAS)



Kingsmore SF et al, Nature Reviews Drug Discovery 2008

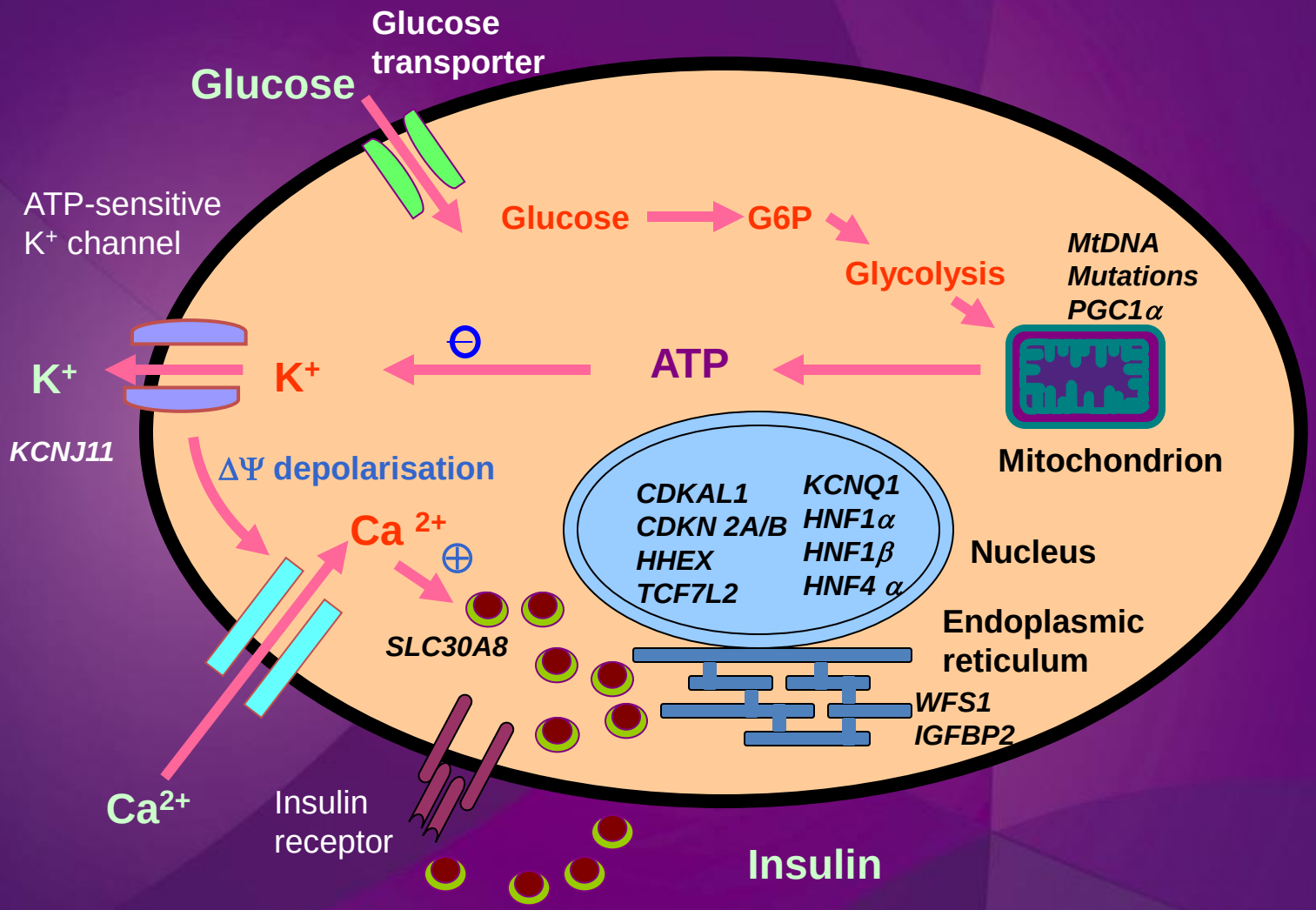
Identified genetic variants for T2 DM



Gene regions as of 7 Nov 2013: >70

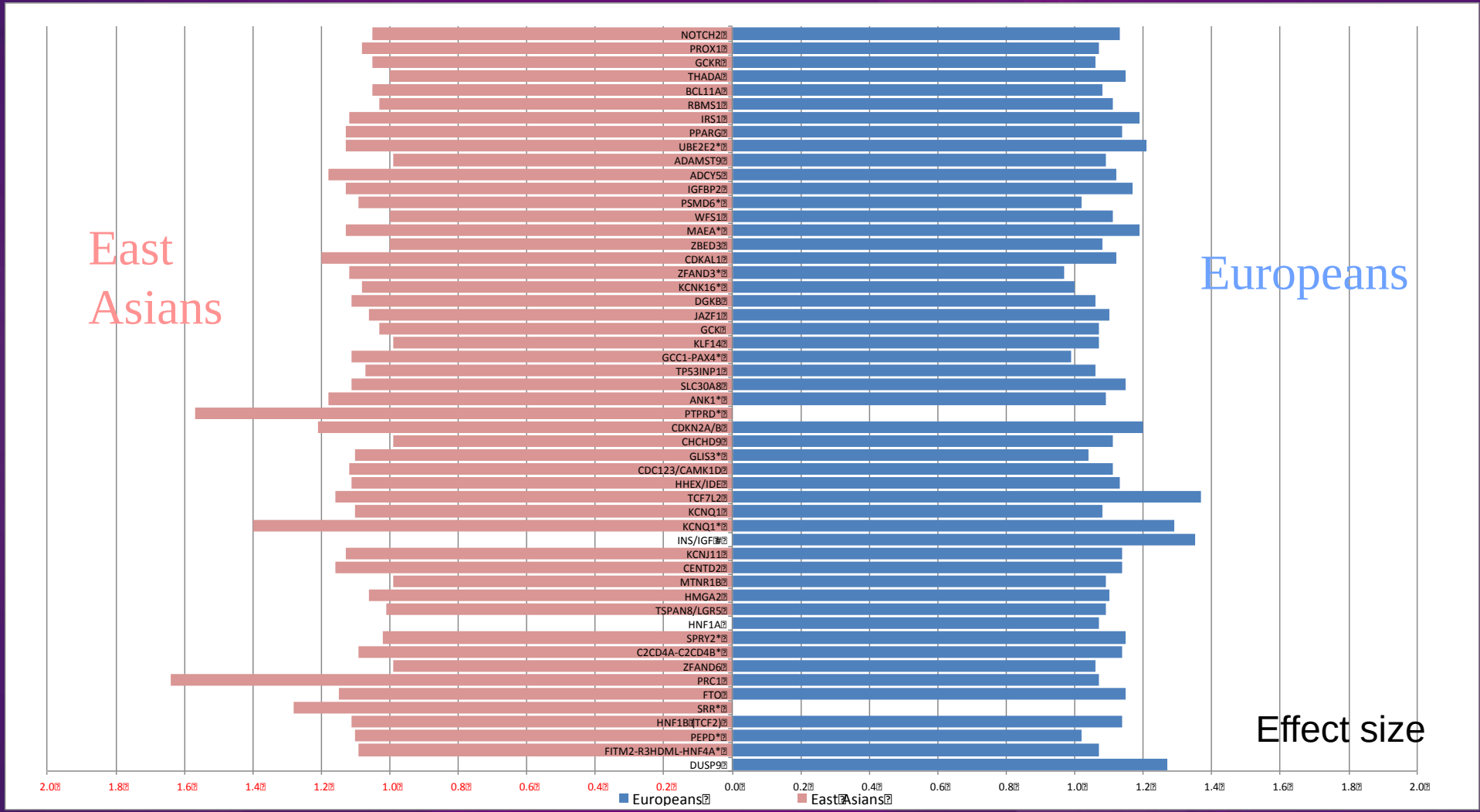
Voigt B et al, Nature Genetics 2010

Biological function of T2 DM variants



Ramachandran A, Ma RC and Snehalatha DC, Lancet 2010; *Jan 30; 375: 408-18*

Genetic markers in E.Asians vs Europeans

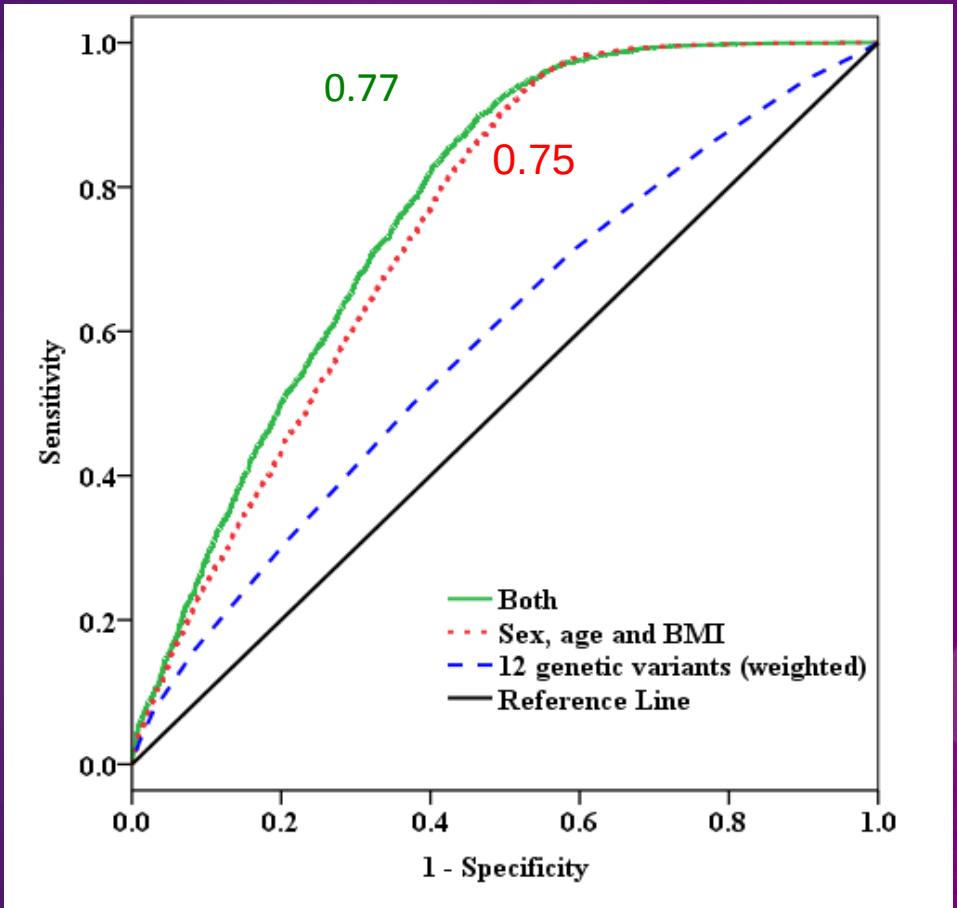


> 60 variants discovered

Ma RC and Chan JC, *Annals NY Acad Sci 2013*

> 70 variants explain

<10% of heritability of T2D



5,882 T2DM a 2,569 healthy controls

Tam CH et al, PLoS One, *in press*

nature genetics

KCNQ1

rs10906115 10p13
rs 1359790 13q31.1

Variants in *KCNQ1* are associated with susceptibility to type 2 diabetes mel

Kazuki Yasuda[1], Kazuaki Miyake[2], Yuk
Yushi Hirota[2], Hiroyuki Mori[2], Anna
He-Yao Wang[1,27], Toshihito Tanahashi
Yasuhiko Iwamoto[12], Yuichiro Yamada
Jun Takeda[3], Eiichi Maeda[15], Hyoung
Maggie C Y Ng[18], Ronald C W Ma[18],
Tiinamaija Tuomi[19,20], Peter Nilsson[21]
Yusuke Nakamura[23], Ken Yamamoto[24]
Hideichi Makino[5], Kishio Nanjo[6], Taka

We carried out a multistage genome-wide as
type 2 diabetes mellitus in Japanese individu
1,612 cases and 1,424 controls and 100,000
significant association was obtained with SN
dense mapping within the gene revealed tha
intron 15 showed the lowest *P* value ($6.7 \times$
(OR) = 1.49). The association of ***KCNQ1*** wi
was replicated in populations of Korean, Chi
ancestry as well as in two independent Japan
and meta-analysis with a total of 19,930 indi
cases and 10,361 controls) yielded a *P* value
(OR = 1.40; 95% CI = 1.34–1.47) for rs223
control subjects, the risk allele of this polym

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Identification of New Genetic Risk Variants for Type 2 Diabetes

Xiao Ou Shu[1]*, Jirong Long[1], Qiuyin Cai[1], Lu Qi[2], Yong-Bing Xiang[3], Yoon Shin Cho[4], E. Shyong Tai[5,6,7], Xiangyang Li[8], Xu Lin[9], Wong-Ho Chow[10], Min Ji, Marilyn C. Cornelis[2], Kai Yu[10], Wanqing Wen[1], Jia, Qibin Qi[2], Hyung-Lae Kim[4], Daniel P. K. Ng[6], Jong, Wei Zheng[1], Frank B. Hu[2]

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Abstract

Although more than 20 genetic susceptibility loci have be
small to moderate effects and account for only a small pr
inter-person genetic variation in this disease remains
association study (GWAS) within the Asian Consortium o
SNPs genotyped in 1,019 T2D cases and 1,710 controls
2,100 SNPs that were not in linkage disequilibrium ($r^2<0.$
conducted among European Americans, Koreans, and Sing
independent set of 1,645 cases and 1,649 controls from Sh
3,316 controls from 2 additional Chinese studies. Cons
(13q31.1), rs10906115 (10p13), and rs1436955 (15q22.2)
1.45×10^{-8} (1.13, 1.08–1.18), and 7.14×10^{-7} (1.13, 1.08–1.
controls. Our study provides strong evidence for a nov
independent risk variants near regions (10p13 and 15q2

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A Genome-Wide Association Study Identifies Susceptibility Variants for Type 2 Diabetes in Han Chinese

Fuu-Jen Tsai[1,2,3*], Chi-Fan Yang[4,5*], Ching-Chu Chen[6,7*], Lee-Ming Chuang[8], Chieh-Hsiang Lu[9], Chwen-Tzuei Chang[6,7], Tzu-Yuan Wang[6,7], Rong-Hsing Chen[6,7], Chiung-Fang Shiu[4], Yi-Min Liu[4], Chih-Chun Chang[4], Pei Chen[4], Chien-Hsiun Chen[4,5], Cathy S. J. Fann[4], Yuan-Tsong Chen[4,5,10*], Jer-Yuarn Wu[4,5,11*]

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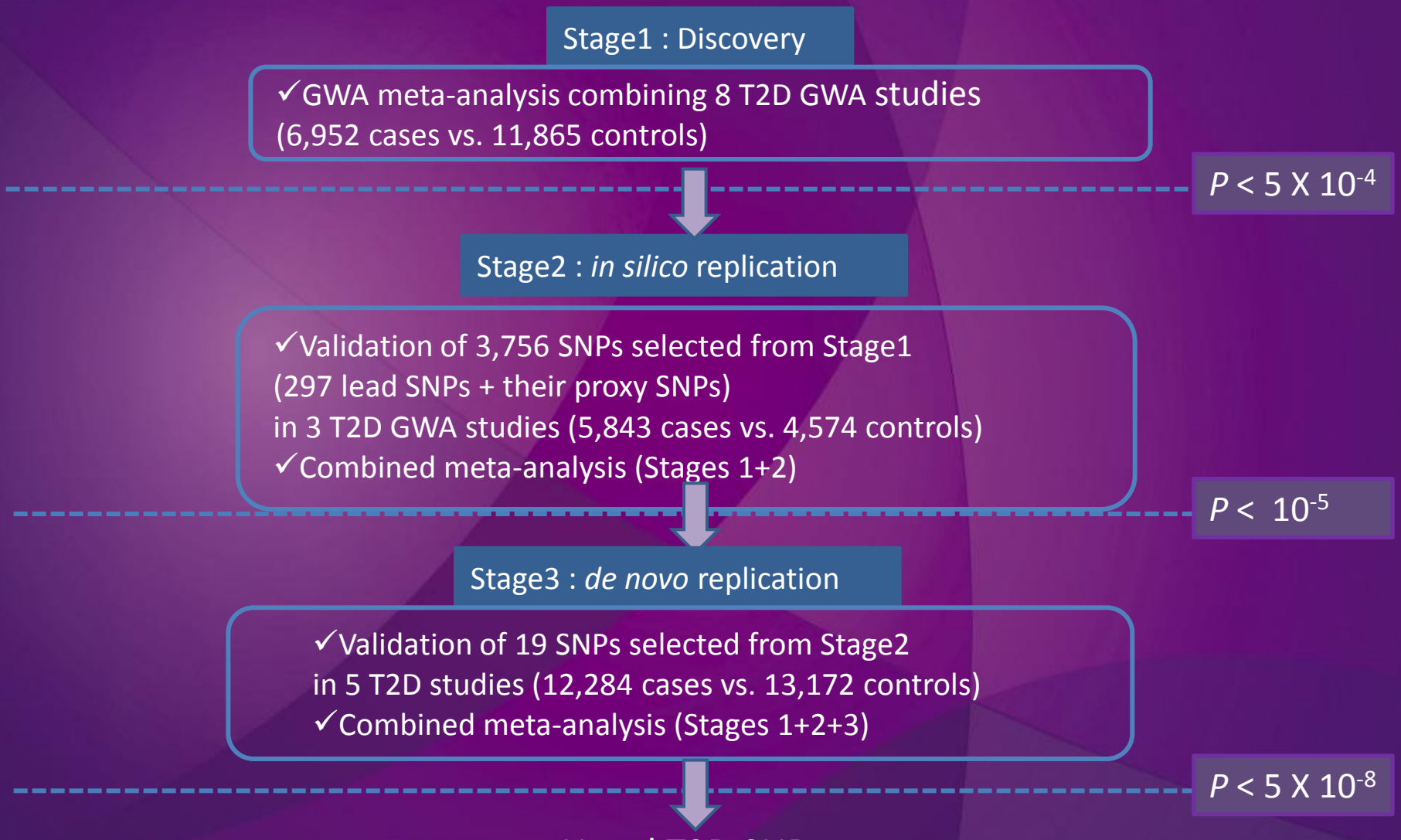
Abstract

To investigate the underlying mechanisms of T2D pathogenesis, we looked for diabetes susceptibility genes that increase the risk of type 2 diabetes (T2D) in a Han Chinese population. A two-stage genome-wide association (GWA) study was conducted, in which 995 patients and 894 controls were genotyped using the Illumina HumanHap550-Duo BeadChip for the first genome scan stage. This was further replicated in 1,803 patients and 1,473 controls in stage 2. We found two loci not previously associated with diabetes susceptibility in and around the genes protein tyrosine phosphatase receptor type D (*PTPRD*) ($P=8.54\times10^{-10}$; odds ratio [OR] = 1.57; 95% confidence interval [CI] = 1.36–1.82), and serine racemase (*SRR*) ($P=3.06\times10^{-9}$; OR = 1.28; 95% CI = 1.18–1.39). We also confirmed that variants in *KCNQ1* were associated with T2D risk, with the strongest signal at rs2237895 ($P=9.65\times10^{-10}$; OR = 1.29, 95% CI = 1.19–1.40). By identifying two novel genetic susceptibility loci in a Han Chinese population and confirming the involvement of *KCNQ1*, which was previously reported to be associated with T2D in Japanese and European descent populations, our results may lead to a better understanding of differences in the molecular pathogenesis of T2D among various populations.

rs17584499 PTPRD
rs391300 SRR

Discovering Asian-relevant Genes Asian GWAS Meta-analysis for T2 DM 25,079 cases and 29,611 controls



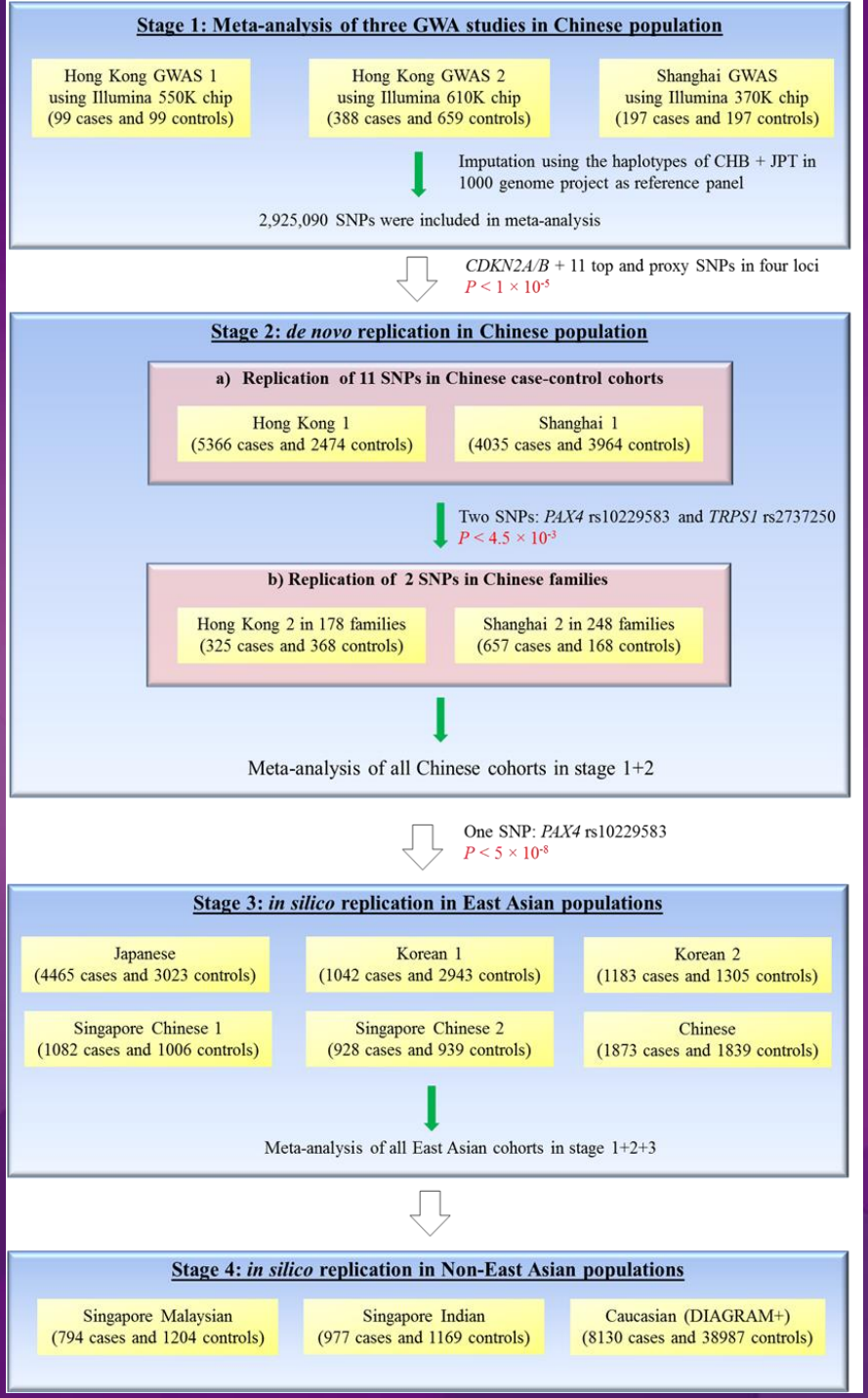
Cho YS et al Nature Genetics 2012

8 novel loci all implicated in beta cell development and protein metabolism

SNP	chr	Loci	Risk allele	OR (CI)	P-value	Possible functions
rs6815464	4	*MAEA*	c	1.13 (1.10-1.16)	1.57E-20	erythroblast enucleation & macrophages maturation
rs7041847	9	*GLIS3*	a	1.10 (1.07-1.13)	1.99E-14	beta cell development and insulin expression
rs6017317	20	*FITM2-R3HDML-HNF4A*	g	1.09(1.07-1.12)	1.12E-11	pancreatic islet development
rs6467136	7	*GCC1*	g	1.11 (1.07-1.14)	4.96E-11	organization of the trans-Golgi network
rs831571	3	*PSMD6*	c	1.09 (1.06-1.12)	8.41E-11	degradation of ubiquitinated proteins
rs9470794	6	*ZFAND3*	c	1.12 (1.08-1.16)	2.06E-10	zinc finger transcription factor
rs3786897	19	*PEPD*	a	1.10 (1.07-1.14)	1.30E-08	Beta cell development
rs1535500	6	*KCNK16*	t	1.08 (1.05-1.11)	2.30E-08	defective regulation of potassium channel activity

Objective

- To identify genetic susceptibility loci in Chinese patients with type 2 diabetes


Stage 1: Meta-analysis of three GWA studies in Chinese population
Hong Kong GWAS 1 using Illumina 550K chip (99 cases and 99 controls)
Hong Kong GWAS 2 using Illumina 610K chip (388 cases and 659 controls)
Shanghai GWAS using Illumina 370K chip (197 cases and 197 controls)
Imputation using the haplotypes of CHB + JPT in 1000 genome project as reference panel
2,925,090 SNPs were included in meta-analysis
CDKN2A/B + 11 top and proxy SNPs in four loci
P < 1 × 10-5
Stage 2: de novo replication in Chinese population
a) Replication of 11 SNPs in Chinese case-control cohorts
Hong Kong 1 (5366 cases and 2474 controls)
Shanghai 1 (4035 cases and 3964 controls)
Two SNPs: PAX4 rs10229583 and TRPS1 rs2737250
P < 4.5 × 10-3
b) Replication of 2 SNPs in Chinese families
Hong Kong 2 in 178 families (325 cases and 368 controls)
Shanghai 2 in 248 families (657 cases and 168 controls)
Meta-analysis of all Chinese cohorts in stage 1+2
One SNP: PAX4 rs10229583
P < 5 × 10-8
Stage 3: in silico replication in East Asian populations
Japanese (4465 cases and 3023 controls)
Korean 1 (1042 cases and 2943 controls)
Korean 2 (1183 cases and 1305 controls)
Singapore Chinese 1 (1082 cases and 1006 controls)
Singapore Chinese 2 (928 cases and 939 controls)
Chinese (1873 cases and 1839 controls)
Meta-analysis of all East Asian cohorts in stage 1+2+3
Stage 4: in silico replication in Non-East Asian populations
Singapore Malaysian (794 cases and 1204 controls)
Singapore Indian (977 cases and 1169 controls)
Caucasian (DIAGRAM+) (8130 cases and 38987 controls)

Study	Cohort	*N* (Male %)	Age (years)	AAD (year)	Diabetes duration (years)	BMI (kg/m^2)	FPG (mmol/l)
Stage 1 (genome scan)							
HK1	Control	99 (36.4)	37.3 ± 10.2	–	–	20.8 ± 2.0	4.7 ± 0.4
	T2D patient	99 (40.4)	40.6 ± 8.8	31.8 ± 7.7	8.0 ± 8.3	30.9 ± 4.4	–
HK2	Diseased control	659 (48.7)	37.1 ± 17.0	–	–	23.3 ± 3.7	–
	T2D patient	388 (49.5)	60.6 ± 10.8	51.1 ± 12.1	9.5 ± 7.0	25.0 ± 3.8	–
SH	Control	197 (50.8)	66.4 ± 10.1	–	–	20.6 ± 1.7	4.8 ± 0.4
	T2D patient	197 (57.9)	41.6 ± 10.4	34.5 ± 4.8	7.3 ± 8.5	23.8 ± 4.1	–
Stage 2 (de novo replication in Chinese)							
HK1	Adolescent control	985 (44.2)	15.5 ± 1.9	–	–	22.7 ± 5.4	4.9 ± 0.4
	Adults control	513 (47.0)	42.0 ± 10.4	–	–	19.9 ± 3.5	4.7 ± 0.3
	Elderly control	976 (51.4)	72.3 ± 5.3	–	–	23.2 ± 3.2	–
	T2D patient	5366 (45.1)	56.7 ± 13.4	48.8 ± 14.9	6.6 ± 6.9	24.6 ± 5.3	–
SH1	Control	3964 (37.6)	51.3 ± 13.5	–	–	23.6 ± 3.2	5.0 ± 0.5
	T2D patient	4035 (52.0)	61.2 ± 12.1	54.2 ± 11.3	7.2 ± 6.9	24.5 ± 3.5	–
HK Family 2	Control	368 (41.0)	37.0 ± 13.6	–	–	24.0 ± 4.1	4.9 ± 0.4
	T2D patient	325 (40.6)	48.0 ± 14.4	41.7 ± 13.1	6.3 ± 7.6	25.9 ± 4.4	–
SH	Control	168 (51.2)	62.8 ± 11.2	–	–	23.7 ± 3.5	4.8 ± 0.6
Family 2	T2D patient	657 (43.7)	54.6 ± 15.6	50.0 ± 14.2	4.9 ± 7.3	23.9 ± 3.5	–

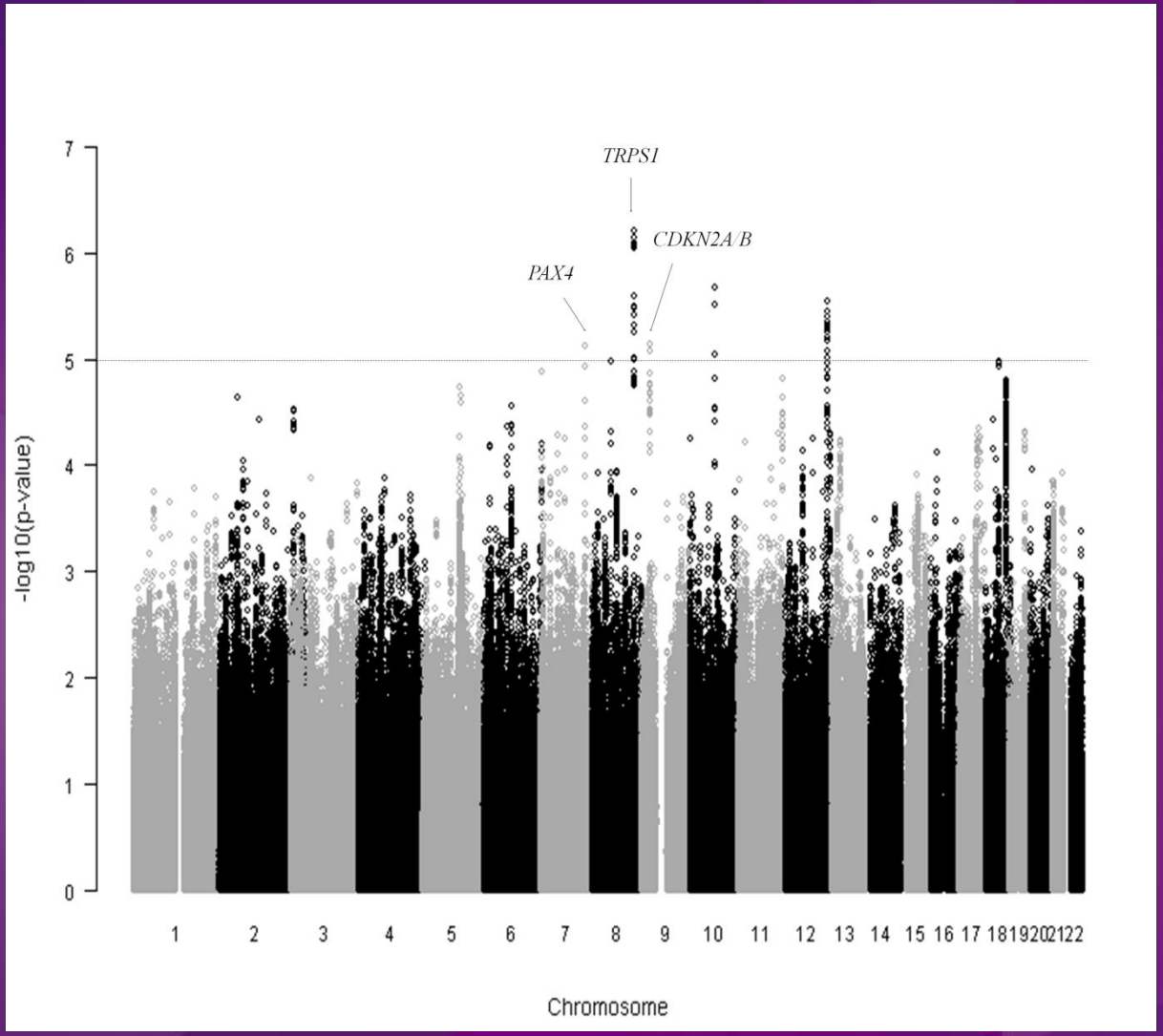

TRPS1
CDKN2A/B
PAX4
-log10(p-value)
0
1
2
3
4
5
6
7
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome

Table 2 Association results for type 2 diabetes (T2D) with 11 top and proxy SNPs in de novo replication stage in Chinese populations

					Hong Kong replication 1 (5,366 T2D vs 2,474 controls)				Shanghai replication 1 (4,035 T2D vs 3,964 controls)				Combined			
SNP	Chromosome	Nearest gene(s)	Position (B36)	Minor/ major allele	Case MAF	Control MAF	OR (95% CI)	$p_{additive}$	Case MAF	Control MAF	OR (95% CI)	$p_{additive}$	OR (95% CI)	p_{meta} (uncorrected)	p_{het}	I^2
rs10229583	7	*PAX4*	127034139	A/G	0.847	0.83	1.14 (1.03, 1.23)	0.0077	0.846	0.825	1.16 (1.08, 1.27)	3.7×10^{-4}	1.15 (1.08, 1.22)	1.0×10^{-5}	0.6406	0.000
rs2721960	8	*TRPS1*	116725904	T/C	0.657	0.644	1.05 (0.98, 1.14)	0.1566	0.655	0.638	1.08 (1.01, 1.15)	0.0277	1.06 (1.02, 1.12)	0.0095	0.7067	0.000
rs2737250	8	*TRPS1*	116731048	G/A	0.631	0.62	1.05 (0.98, 1.12)	0.1807	0.641	0.621	1.09 (1.02, 1.16)	0.0090	1.08 (1.02, 1.12)	0.0045	0.4582	0.000
rs3858158	10	*COL13A1*	71310056	C/T	0.516	0.521	0.98 (0.92, 1.05)	0.6000	0.569	0.561	1.03 (0.97, 1.10)	0.3211	1.01 (0.96, 1.05)	0.7408	0.3026	0.506
rs2395272	10	*COL13A1*	71310261	A/G	0.531	0.534	0.99 (0.93, 1.06)	0.7680	0.594	0.584	1.04 (0.97, 1.11)	0.2312	1.02 (0.97, 1.06)	0.4589	0.3027	0.364
rs57703465	10	*COL13A1*	71311074	T/C	0.654	0.662	0.96 (0.89, 1.04)	0.3463	0.667	0.656	1.05 (0.98, 1.12)	0.1502	1.01 (0.96, 1.06)	0.6467	0.0976	0.765
rs11065441	12	*P2RX7*	120045354	C/T	0.728	0.724	1.02 (0.94, 1.11)	0.6224	0.728	0.733	0.97 (0.91, 1.04)	0.4312	0.99 (0.94, 1.05)	0.7756	0.3748	0.000
rs684201	12	*P2RX7*	120054726	A/G	0.73	0.726	1.02 (0.94, 1.10)	0.5916	0.735	0.739	0.98 (0.91, 1.05)	0.5609	1.00 (0.94, 1.05)	0.9462	0.4332	0.000
rs11065450	12	*P2RX7*	120064040	A/C	0.682	0.688	0.97 (0.90, 1.05)	0.4995	0.702	0.707	0.98 (0.92, 1.05)	0.5520	0.98 (0.93, 1.03)	0.3699	0.9111	0.000
rs208290	12	*P2RX7*	120078439	T/C	0.612	0.609	1.01 (0.94, 1.09)	0.7086	0.643	0.645	0.99 (0.93, 1.06)	0.7950	1.00 (0.95, 1.05)	0.9605	0.6472	0.000
rs10849851	12	*P2RX7*	120081027	G/A	0.727	0.72	1.03 (0.95, 1.12)	0.4079	0.737	0.741	0.98 (0.91, 1.05)	0.5237	1.00 (0.95, 1.05)	0.9308	0.3002	0.068

Nearest Entrez genes within 250 kb

p, p_{meta} and p_{het} represent p values from logistic regression without any adjustment under the additive genetic model, meta-analysis under a fixed effect model (uncorrected for multiple testing) and test of heterogeneity, respectively

ORs are reported with respect to the minor allele

Study	Cohort	*N* (Male %)	Age (years)	AAD (year)	Diabetes duration (years)	BMI (kg/m^2)	FPG (mmol/l)
Stage 3 (in silico replication in East Asians)							
Japanese	Control	3023 (54.5)	51.9 ± 15.2	–	–	22.4 ± 3.7	–
	T2D patient	4465 (68.0)	65.8 ± 10.0	56.5 ± 11.4	9.4 ± 8.4	24.1 ± 3.8	–
Korean 1	Control	2943 (46.0)	51.1 ± 8.6	–	–	24.1 ± 3.0	4.5 + 0.4
	T2D patient	1042 (51.7)	56.4 ± 8.6	–	–	25.5 ± 3.3	7.0 ± 2.6
Korean 2	Control	1305 (54.5)	65.2 ± 2.6	–	–	23.9 ± 3.0	5.0 ± 0.5
	T2D patient	1183 (46.5)	58.6 ± 7.1	–	–	25.2 ± 3.4	7.4 ± 2.7
Singapore Chinese 1	Control	1006 (21.6)	47.7 ± 11.1	–	–	22.3 ± 3.7	4.7 ± 0.4
	T2D patient	1082 (37.2)	65.1 ± 9.7	55.7 ± 12.0	–	25.3 ± 3.9	–
Singapore Chinese 2	Control	939 (63.8)	46.7 ± 10.2	–	–	22.8 ± 3.4	4.7 ± 0.5
	T2D patient	928 (64.9)	63.7 ± 10.8	52.2 ± 14.4	–	25.4 ± 3.8	–
Chinese	Control	1839 (43.7)	54.1 ± 9.2	–	–	24.00 ± 3.18	5.04 ± 0.35
	T2D patient	1873 (46.0)	58.6 ± 8.4	–	–	25.00 ± 3.24	8.43 ± 2.90

Identification of novel T2D loci in Chinese

Stage 1: Meta-analysis of GWAS in Chinese
684 T2 DM cases: 955 controls

Stage 2: *de novo* replication in Chinese
11067 T2 DM: 7929 controls

Stage 3: *in silico* replication in East Asians
10573 T2 DM: 11055 controls

Stage 4*: in silico* replication in other populations
9901 T2 DM: 41360 controls

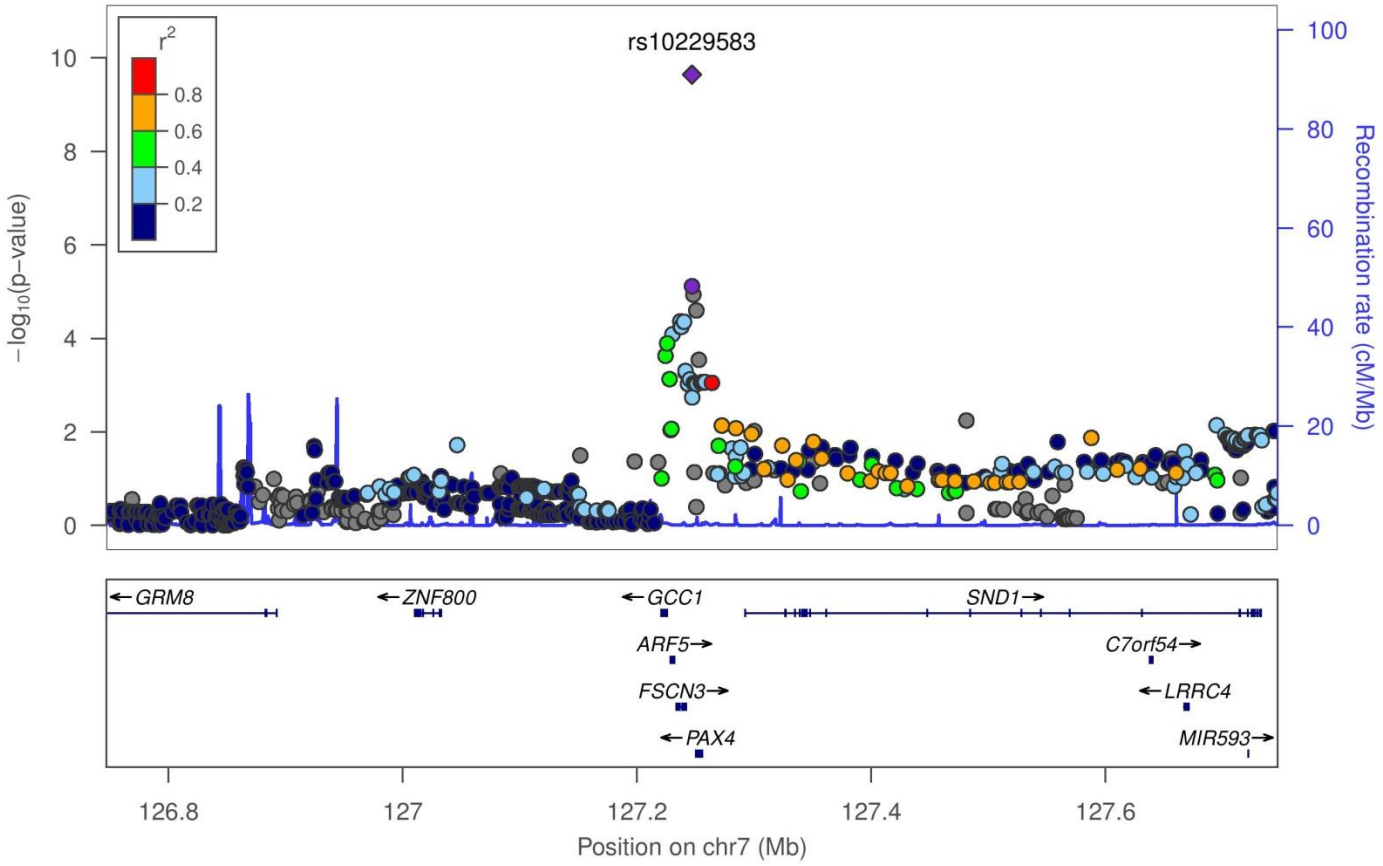
Global meta-analysis of stages 1+2+3+4
31541 cases: 60344 controls

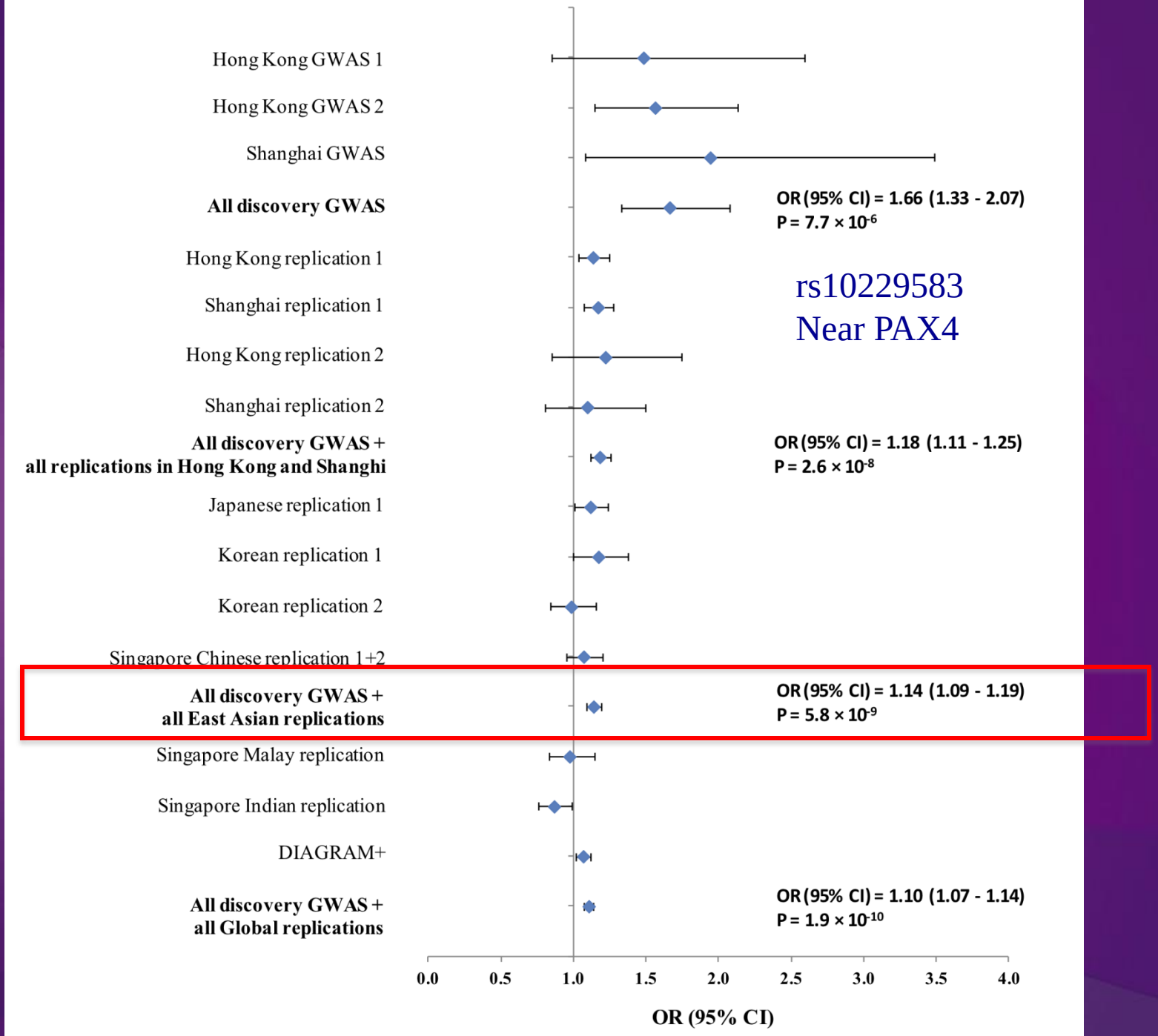
Stage	Cohort	Adjustment	*N*		Risk allele frequencies					
			T2D	Control	T2D	Control	OR (95% CI)	$p_{additive}$ (uncorrected GC)	p_{het}	I^2
1. Discovery	Hong Kong GWAS 1	Sex and age	99	99	0.879	0.818	1.48 (0.85, 2.59)	0.1645		
	Hong Kong GWAS 2	Sex and age	388	659	0.857	0.820	1.56 (1.14, 2.13)	0.0055		
	Shanghai GWAS	None	197	197	0.873	0.777	1.92 (1.32, 2.79)	5.0×10^{-4}		
	Meta-analysis of GWAS		684	955			1.66 (1.33, 2.07)	7.7×10^{-6}	0.6455	0.000
2. De novo replications in Hong Kong and Shanghai	Hong Kong replication 1	None	5,366	2,474	0.847	0.831	1.13 (1.03, 1.24)	7.7×10^{-3}		
	Shanghai replication 1	None	4,035	3,964	0.846	0.825	1.17 (1.07, 1.27)	3.7×10^{-4}		
	Hong Kong family replication 2	Sex and age	325	368	0.872	0.856	1.22 (0.85, 1.74)	0.2817		
	Shanghai family replication 2	Sex and age	657	168	0.824	0.813	1.09 (0.80, 1.49)	0.5757		
	Replication in Chinese		10,383	6,974			1.15 (1.08, 1.22)	1.0×10^{-5}	0.6406	0.000
	Meta-analysis of Chinese		11,067	7,929			1.18 (1.11, 1.25)	2.6×10^{-8}	0.0839	0.596
3. In silico replications in East Asians	Japanese replication	None	4,465	3,023	0.892	0.881	1.11 (1.01, 1.23)	0.0379		
	Korean replication 1	None	1,042	2,943	0.894	0.878	1.17 (0.99, 1.38)	0.0577		
	Korean replication 2	None	1,183	1,305	0.841	0.844	0.98 (0.84, 1.15)	0.8101		
	Singapore Chinese replication 1	None	1,082	1,006	0.832	0.819	1.07 (0.95, 1.20)	0.2728		
	Singapore Chinese replication 2	None	928	939	0.833	0.816				
	Chinese replication	First 2 PCs	1,873	1,839	0.8396	0.8167	1.17 (1.04, 1.32)	0.01091		
	Replication in other East Asian		10,573	11,055			1.10 (1.04, 1.17)	6.0×10^{-4}	0.6767	0.000
	Meta-analysis of East Asian		21,640	18,984			1.14 (1.09, 1.19)	2.3×10^{-10}	0.5939	0.000
4. In silico replications in South Asians and Europeans	Singapore Malaysian replication	None	794	1,204	0.798	0.804	0.97 (0.83, 1.14)	0.7185		
	Singapore Indian replication	None	977	1,169	0.647	0.682	0.86 (0.76, 0.98)	0.0276		
	DIAGRAM	None	8,130	38,987	–	–	1.06 (1.02, 1.12)	8.6×10^{-3}		
	Replication in non-East Asian		9,901	41,360			1.03 (0.99, 1.08)	0.1156	0.0042	0.878

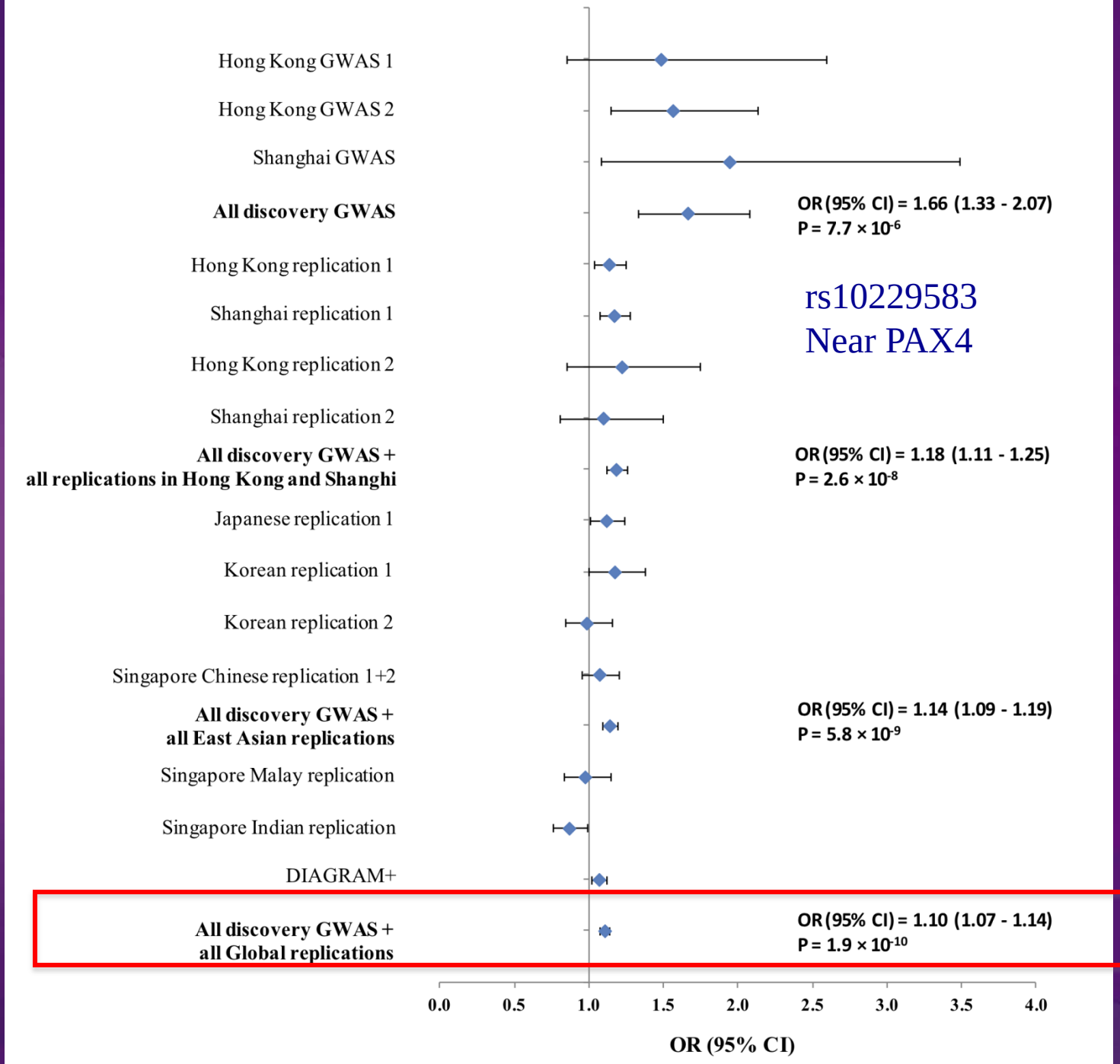
ORs and 95% CIs were reported with respect to the T2D-related risk alleles (G)

p_{het} refers to the p value obtained from the heterogeneity test

GC, genomic control; PC, principal components


rs10229583
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
GRM8
ZNF800
GCC1
SND1
ARF5
C7orf54
FSCN3
LRRC4
PAX4
MIR593
126.8
127
127.2
127.4
127.6
Position on chr7 (Mb)


Hong Kong GWAS 1
Hong Kong GWAS 2
Shanghai GWAS
All discovery GWAS
OR (95% CI) = 1.66 (1.33 - 2.07)
P = 7.7 × 10-6
Hong Kong replication 1
Shanghai replication 1
Hong Kong replication 2
Shanghai replication 2
rs10229583
Near PAX4
All discovery GWAS +
all replications in Hong Kong and Shanghi
OR (95% CI) = 1.18 (1.11 - 1.25)
P = 2.6 × 10-8
Japanese replication 1
Korean replication 1
Korean replication 2
Singapore Chinese replication 1+2
All discovery GWAS +
all East Asian replications
OR (95% CI) = 1.14 (1.09 - 1.19)
P = 5.8 × 10-9
Singapore Malay replication
Singapore Indian replication
DIAGRAM+
All discovery GWAS +
all Global replications
OR (95% CI) = 1.10 (1.07 - 1.14)
P = 1.9 × 10-10
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
OR (95% CI)

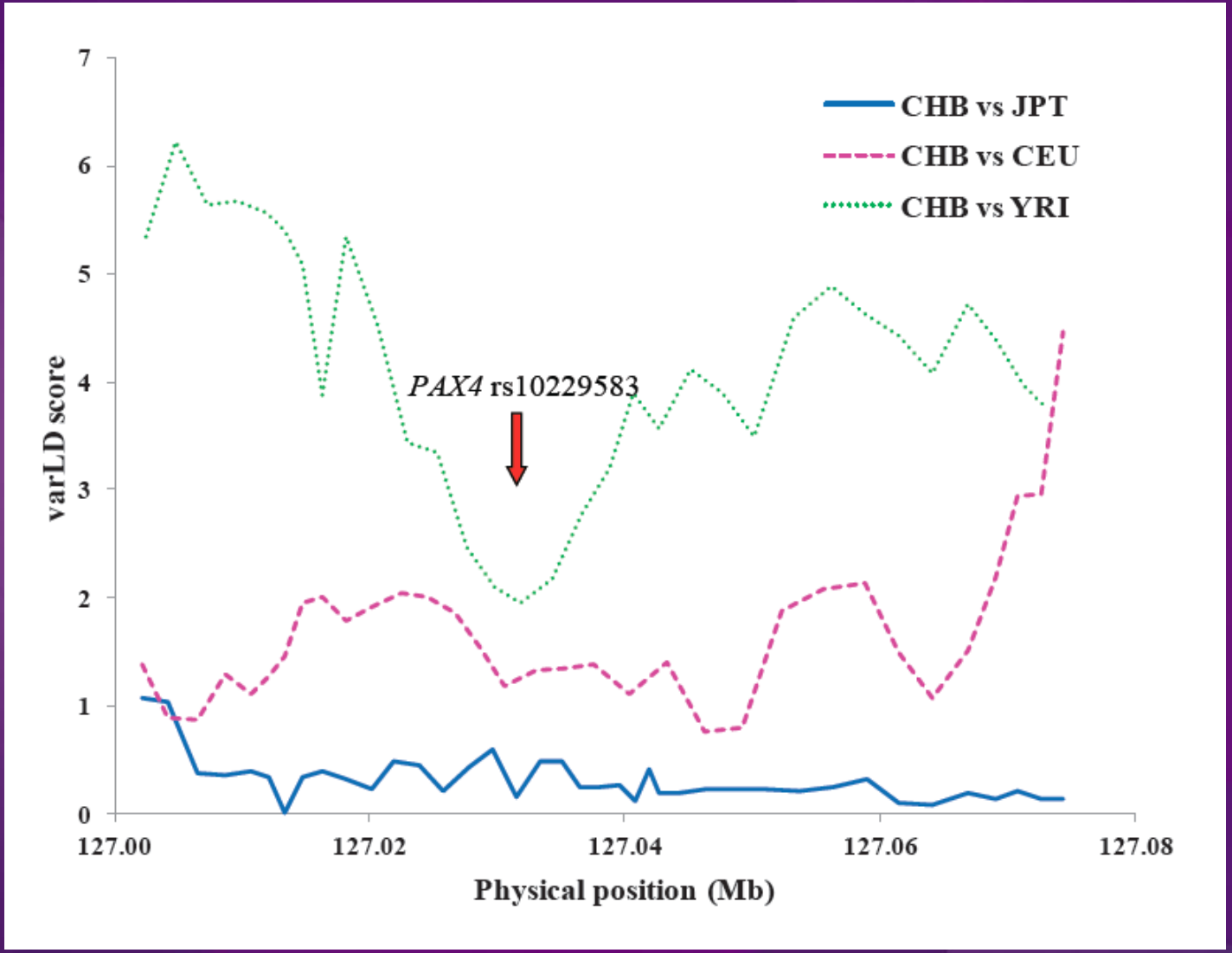

Hong Kong GWAS 1
Hong Kong GWAS 2
Shanghai GWAS
All discovery GWAS
OR (95% CI) = 1.66 (1.33 - 2.07)
P = 7.7 × 10-6
Hong Kong replication 1
Shanghai replication 1
Hong Kong replication 2
Shanghai replication 2
rs10229583
Near PAX4
All discovery GWAS +
all replications in Hong Kong and Shanghi
OR (95% CI) = 1.18 (1.11 - 1.25)
P = 2.6 × 10-8
Japanese replication 1
Korean replication 1
Korean replication 2
Singapore Chinese replication 1+2
All discovery GWAS +
all East Asian replications
OR (95% CI) = 1.14 (1.09 - 1.19)
P = 5.8 × 10-9
Singapore Malay replication
Singapore Indian replication
DIAGRAM+
All discovery GWAS +
all Global replications
OR (95% CI) = 1.10 (1.07 - 1.14)
P = 1.9 × 10-10
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
OR (95% CI)

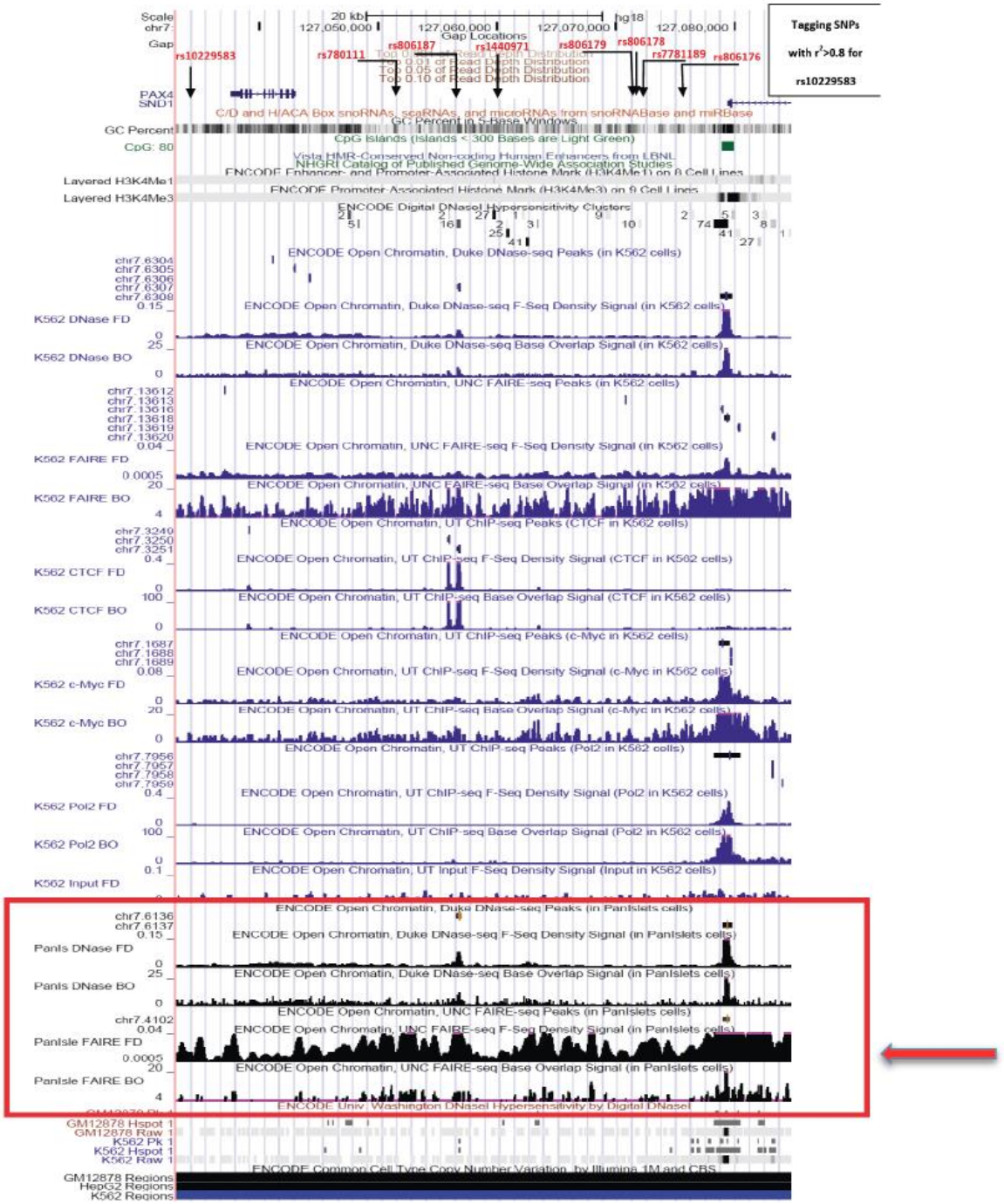
Heterogeneity in effects between East Asians and other populations

Population	OR (95% CI)	Heterogeneity of OR	
		Q test *P*	I^2
Chinese	1.18 (1.11, 1.25)	--	--
Japanese + Korean	1.09 (1.01, 1.18)	0.1254	0.5742
DIAGRAM+	1.06 (1.02, 1.12)	0.0088	0.8544
Malaysian + Indian	0.90 (0.82, 1.00)	1.1×10^{-5}	0.9485

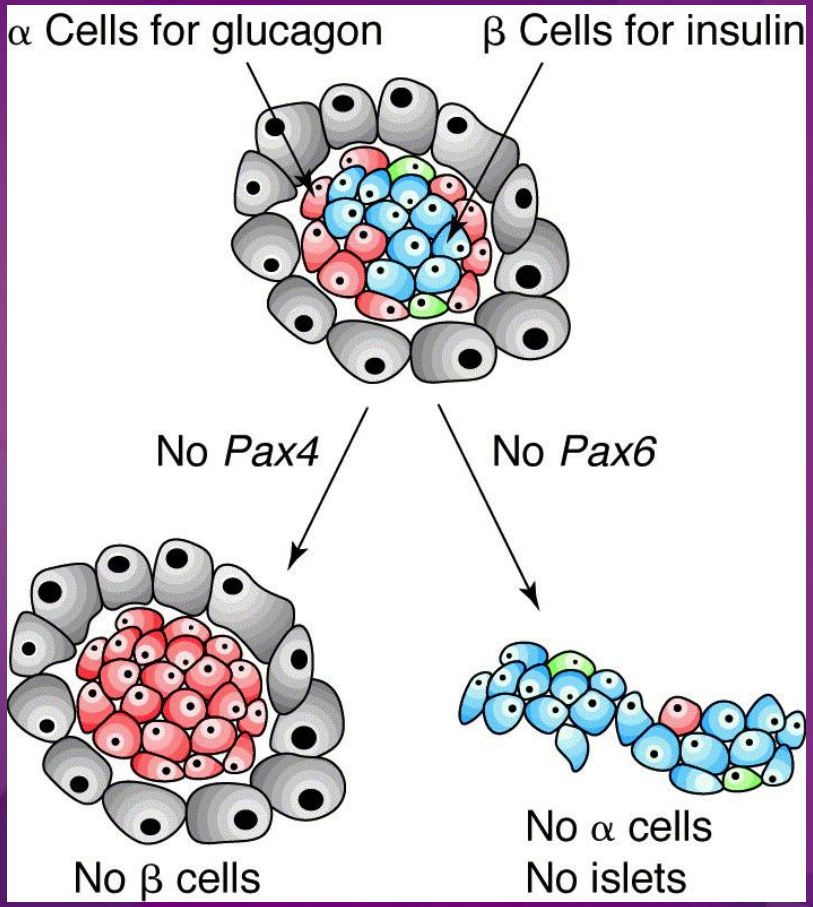
Q test *P* and I^2 refer to the statistical significance and quantified index of heterogeneity test of OR between Chinese and other populations, respectively.

Significant Variation in LD and genetic architecture around the identified loci



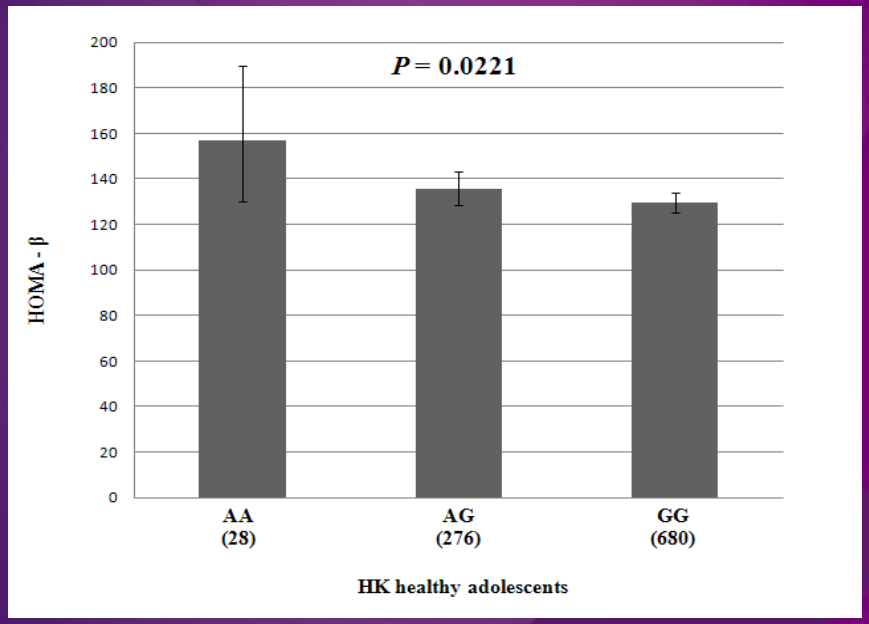

Tagging SNPs
with r²>0.8 for
rs10229583
Scale
chr7:
Gap
20 kb
127,050,000
127,060,000
127,070,000
127,080,000
hg18
Gap Locations
rs10229583
rs780111
rs806187
rs1440971
rs806179
rs806178
rs7781189
rs806176
Top 0.01 of Read Depth Distribution
Top 0.05 of Read Depth Distribution
Top 0.10 of Read Depth Distribution
PAX4
SND1
C/D and H/ACA Box snoRNAs, scaRNAs, and microRNAs from snoRNABase and miRBase
GC Percent
GC Percent in 5-Base Windows
CpG: 80
CpG Islands (Islands < 300 Bases are Light Green)
Vista HMR-Conserved Non-coding Human Enhancers from LBNL
NHGRI Catalog of Published Genome-Wide Association Studies
ENCODE Enhancer- and Promoter-Associated Histone Mark (H3K4Me1) on 9 Cell Lines
Layered H3K4Me1
ENCODE Promoter-Associated Histone Mark (H3K4Me3) on 9 Cell Lines
Layered H3K4Me3
ENCODE Digital DNaseI Hypersensitivity Clusters
ENCODE Open Chromatin, Duke DNase-seq Peaks (in K562 cells)
chr7.6304
chr7.6305
chr7.6306
chr7.6307
chr7.6308
ENCODE Open Chromatin, Duke DNase-seq F-Seq Density Signal (in K562 cells)
0.15
K562 DNase FD
0
ENCODE Open Chromatin, Duke DNase-seq Base Overlap Signal (in K562 cells)
25
K562 DNase BO
0
ENCODE Open Chromatin, UNC FAIRE-seq Peaks (in K562 cells)
chr7.13612
chr7.13613
chr7.13616
chr7.13618
chr7.13619
chr7.13620
ENCODE Open Chromatin, UNC FAIRE-seq F-Seq Density Signal (in K562 cells)
0.04
K562 FAIRE FD
0.0005
ENCODE Open Chromatin, UNC FAIRE-seq Base Overlap Signal (in K562 cells)
20
K562 FAIRE BO
4
ENCODE Open Chromatin, UT ChIP-seq Peaks (CTCF in K562 cells)
chr7.3249
chr7.3250
chr7.3251
ENCODE Open Chromatin, UT ChIP-seq F-Seq Density Signal (CTCF in K562 cells)
0.4
K562 CTCF FD
0
ENCODE Open Chromatin, UT ChIP-seq Base Overlap Signal (CTCF in K562 cells)
100
K562 CTCF BO
0
ENCODE Open Chromatin, UT ChIP-seq Peaks (c-Myc in K562 cells)
chr7.1687
chr7.1688
chr7.1689
ENCODE Open Chromatin, UT ChIP-seq F-Seq Density Signal (c-Myc in K562 cells)
0.08
K562 c-Myc FD
0
ENCODE Open Chromatin, UT ChIP-seq Base Overlap Signal (c-Myc in K562 cells)
20
K562 c-Myc BO
0
ENCODE Open Chromatin, UT ChIP-seq Peaks (Pol2 in K562 cells)
chr7.7956
chr7.7957
chr7.7958
chr7.7959
ENCODE Open Chromatin, UT ChIP-seq F-Seq Density Signal (Pol2 in K562 cells)
0.4
K562 Pol2 FD
0
ENCODE Open Chromatin, UT ChIP-seq Base Overlap Signal (Pol2 in K562 cells)
100
K562 Pol2 BO
0
ENCODE Open Chromatin, UT Input F-Seq Density Signal (Input in K562 cells)
0.1
K562 Input FD
ENCODE Open Chromatin, Duke DNase-seq Peaks (in PanIslets cells)
chr7.6136
chr7.6137
ENCODE Open Chromatin, Duke DNase-seq F-Seq Density Signal (in PanIslets cells)
0.15
PanIs DNase FD
0
ENCODE Open Chromatin, Duke DNase-seq Base Overlap Signal (in PanIslets cells)
25
PanIs DNase BO
0
ENCODE Open Chromatin, UNC FAIRE-seq Peaks (in PanIslets cells)
chr7.4102
ENCODE Open Chromatin, UNC FAIRE-seq F-Seq Density Signal (in PanIslets cells)
0.04
PanIsle FAIRE FD
0.0005
ENCODE Open Chromatin, UNC FAIRE-seq Base Overlap Signal (in PanIslets cells)
20
PanIsle FAIRE BO
4
ENCODE Univ. Washington DNaseI Hypersensitivity by Digital DNaseI
GM12878 Hspot 1
GM12878 Raw 1
K562 Pk 1
K562 Hspot 1
K562 Raw 1
ENCODE Common Cell Type Copy Number Variation, by Illumina 1M and CBS
GM12878 Regions
HepG2 Regions
K562 Regions

Function of PAX4

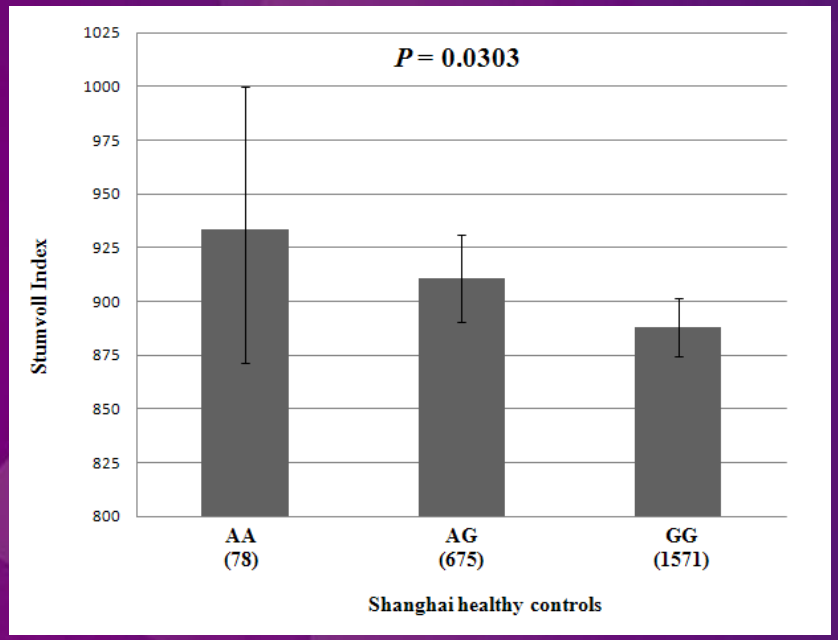


Non-diabetic carriers of the risk variant had impaired beta-cell function

Healthy adolescents in HK



Shanghai healthy controls



Associated with earlier age of diagnosis among Chinese with T2DM:
$P=2.3\times10^{-4}$, $\beta_{unadjusted} \pm SE = -0.90 \pm 0.24$)

Ma RC, Hu C et al, *Diabetologia 2013*

Summary

- GWAS meta-analysis in Chinese patients with T2DM identified a novel loci for T2DM
- Non-diabetic individuals who carry the risk variant have evidence of impaired beta-cell function
- The variant resides in a region of genetic variability

Diabetologia (2013) 56:1291–1305
DOI 10.1007/s00125-013-2874-4

ARTICLE

Genome-wide association study in a Chinese population identifies a susceptibility locus for type 2 diabetes at 7q32 near *PAX4*

R. C. W. Ma · C. Hu · C. H. Tam · R. Zhang · P. Kwan · T. F. Leung · G. N. Thomas · M. J. Go · K. Hara · X. Sim · J. S. K. Ho · C. Wang · H. Li · L. Lu · Y. Wang · J. W. Li · Y. Wang · V. K. L. Lam · J. Wang · W. Yu · Y. J. Kim · D. P. Ng · H. Fujita · K. Panoutsopoulou · A. G. Day-Williams · H. M. Lee · A. C. W. Ng · Y-J. Fang · A. P. S. Kong · F. Jiang · X. Ma · X. Hou · S. Tang · J. Lu · T. Yamauchi · S. K. W. Tsui · J. Woo · P. C. Leung · X. Zhang · N. L. S. Tang · H. Y. Sy · J. Liu · T. Y. Wong · J. Y. Lee · S. Maeda · G. Xu · S. S. Cherny · T. F. Chan · M. C. Y. Ng · K. Xiang · A. P. Morris · DIAGRAM Consortium · S. Keildson · The MuTHER Consortium · R. Hu · L. Ji · X. Lin · Y. S. Cho · T. Kadowaki · E. S. Tai · E. Zeggini · M. I. McCarthy · K. L. Hon · L. Baum · B. Tomlinson · W. Y. So · Y. Bao · J. C. N. Chan · W. Jia

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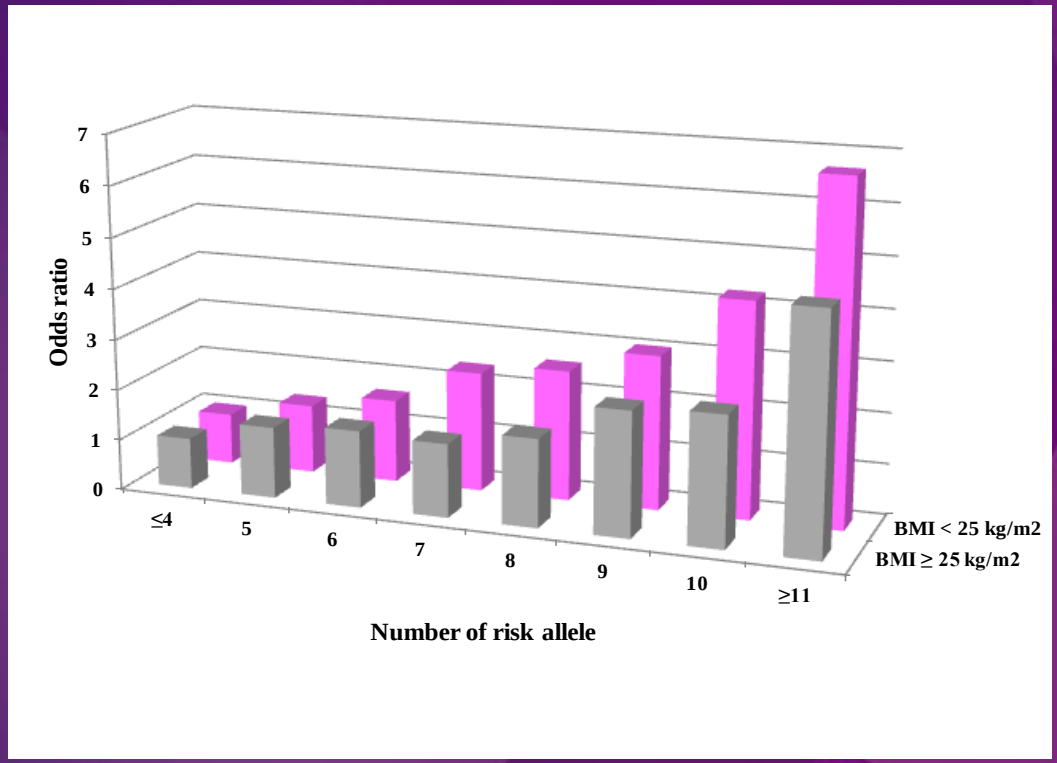
Targeted re-sequencing studies of PAX4 region

Utilization of genetic score for T2DM



CGS from 8 loci:

IGF2BP2 rs4402960,
WFS1 rs734312,
CDKAL1 rs7756992,
SLC30A8 rs13266634,
CDKN2A/B rs10811661,
HHEX rs7923837,
TCF7L2 rs7903146
KCNQ1 rs2237892

Controls: increasing number of risk alleles for CGS asso with lower HOMA-beta
For T2DM: increasing number of risk alleles asso with lower BMI, WC
Increasing alleles asso with younger age of onset of T2DM
Increasing numbers of alleles also asso. with insulin use at time of recruitment

Tam CH et al, *PLoS One, in press*

Conclusions

- Genome-wide association study in Chinese have identified a novel locus for T2DM
- The risk variant is associated with reduced beta-cell function and earlier age of onset in Asians
- Targeted re-sequencing has identified additional variants within the region
- Incorporation of genetic markers to improved prediction of treatment outcome

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Xiaodan Fan
Nelson Tang
Wing Yee So
+ Many others
Medical and nursing staff of DM centre

UGC 大學教育資助委員會 University Grants Committee

Innovation and Technology Fund
Innovation and Technology Commission
The Government of the Hong Kong Special Administrative Region

EFSD European Foundation for the Study of Diabetes

NIDDK NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

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