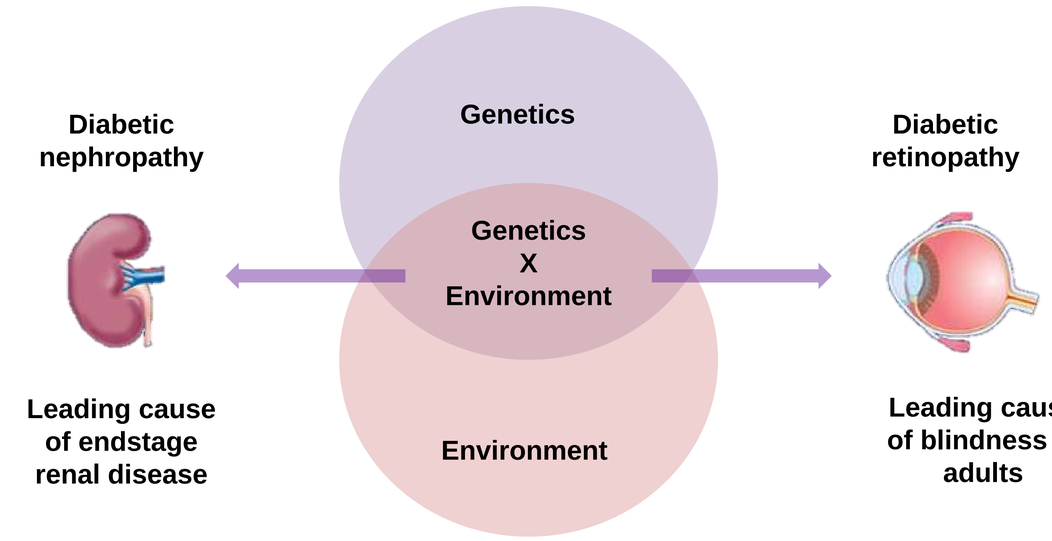
Diabetic retinopathy genetic variants identified in genome-wide association studies and the risk of microvascular complications in Chinese diabetic patients

Chloe YY Cheung[1], Elaine YL Hui[1], Kelvin HM Kwok[1], Carol HY Fong[1], Rachel LC Wong[1], Chi Ho Lee[1], Michele Yuen[1], Yu Cho Woo[1], Chun Yip Yeung[1], Wing Sun Chow[1], Pak C Sham[2,4], and Karen SL Lam[1,3]

[1]Department of Medicine and [2]Department of Psychiatry, [3]Research Centre of Heart, Brain, Hormone and Healthy Aging, the [4]Centre for Genomic Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong.

Introduction



- Diabetic retinopathy (DR) and diabetic nephropathy (DN) are multifactoral diseases caused by complex interactions between multiple genetic and environmental factors.
- Understanding the genetic basis of these diseases may serve to identify the possible common underlying pathophysiology mechanisms.
- This genetic information may also contribute to the risk profiling of chronic microangiopathic complications in diabetic patients, which may be useful in facilitating their early diagnosis.
- Findings from genome-wide association studies (GWAS) provide novel insights into the pathogenesis of various diseases.
- Recent GWAS identified novel susceptibility genetic variants for DR[1-4] which deserve further investigation.

Objectives

- This study aimed (i) to validate the associations of these genetic variants with DR and (ii) to evaluate whether these DR-associated SNPs would also be associated with an increased risk of DN, in Chinese diabetic patients.

Methods & Materials

- **Study design**

✓ Three cross-sectional case-control studies on **(1) sight-threatening DR (STDR); (2) proliferative DR (PDR); and (3) DN**, were performed based on subjects from the Hong Kong West Diabetes Registry.

- **Subjects**

✓ **STDR cases (n=576):** Based on the United Kingdom National Screening Committee classification protocol for grading of retinopathy, patients having PDR (R3), or severe pre-PDR (R2), or having clinically significant macular oedema (CSMO), were considered as STDR cases.

✓ **PDR cases (n=309):** Patients graded retinopathy level R3 were considered as PDR cases.

✓ **DN cases (n=984):** DN cases included patients with the presence of either microalbuminuria or macroalbuminuria, as indicated by the patient's urinary albumin-to-creatinine ratio (ACR) in two random urine samples, collected within 6 months, according to the American Diabetes Association criteria.

✓ **Non-DR & non-DN controls (n=1055):** Subjects with normoalbuminuria (NA) and no retinopathy (R0) were considered as controls.

- **Single nucleotide polymorphisms (SNPs) selection**

✓ 36 top associated SNPs ($P<5x10^{-4}$, $r^2<0.9$) previously identified in DR GWAS were selected for investigation.

✓ 4 monomorphic SNPs and 5 SNPs which failed to pass quality check (deviation from Hardy-Weinberg Equilibrium or genotyping call rate < 90%) were excluded from analyses.

- **Statistical analysis**

✓ Binary logistic regression analyses, with adjustment for age, duration of diabetes, gender, systolic blood pressure, diastolic blood pressure, and HbA1c, were used to evaluate the independent associations of SNPs with DR and DN.

Results

Table 1. Association analyses of GWAS identified DR-associated SNPs with STDR, PDR and DN.

				STDR 576 cases vs 1055 controls		PDR 309 cases vs 1055 controls		DN 984 cases vs 1055 controls	
CHR	SNP	Nearest Gene(s)	A1	OR(95%CI)	$P_{adjusted}$*	OR(95%CI)	$P_{adjusted}$*	OR(95%CI)	$P_{adjusted}$*
1	rs3007729	*IGSF21-KLHDC7A*	T	0.93(0.78-1.12)	0.463	0.94(0.75-1.18)	0.599	1.01(0.87-1.17)	0.948
1	rs2811893	*MYSM1*	C	1.05(0.88-1.26)	0.563	1.03(0.82-1.28)	0.813	1.06(0.92-1.23)	0.397
1	rs1342038	*TNFSF4-RPL26P11*	C	0.91(0.77-1.08)	0.300	0.88(0.71-1.08)	0.225	0.92(0.80-1.06)	0.246
1	rs6662352	*KIAA1804-KCNK1*	T	1.01(0.84-1.21)	0.915	0.91(0.72-1.14)	0.406	1.09(0.94-1.26)	0.246
1	rs10927101	*AKT3-ZNF238*	C	1.09(0.91-1.31)	0.355	1.13(0.90-1.42)	0.301	0.99(0.85-1.15)	0.873
1	rs476141	*AKT3 and ZNF238*	A	0.90(0.73-1.11)	0.312	0.91(0.70-1.19)	0.496	0.96(0.85-1.14)	0.624
2	**rs10199521**	***MYT1L-TSSC1***	**A**	1.13(0.96-1.35)	0.150	**1.34(1.09-1.67)**	**$6.8x10^{-3}$**	1.07(0.92-1.23)	0.389
2	rs1399634	*LRP2-BBS5*	T	1.00(0.84-1.19)	0.982	1.04(0.84-1.29)	0.733	0.99(0.86-1.15)	0.930
3	**rs13064954**	***LEKR1-CCNL1***	**A**	1.32(0.97-1.78)	0.077	1.20(0.81-1.76)	0.364	**1.46(1.14-1.86)**	**$2.5x10^{-3}$**
3	**rs9866141**	***KRT18P34-VEPH1***	**T**	**1.50(1.10-2.05)**	**0.010**	1.37(0.93-2.02)	0.116	**1.57(1.22-2.02)**	**$5.4x10^{-4}$**
4	rs4470583	*RPS14P7-FSTL5*	A	0.85(0.61-1.18)	0.329	0.89(0.59-1.33)	0.553	0.92(0.70-1.19)	0.510
5	rs17376456	*C5orf36*	G	0.81(0.53-1.24)	0.326	0.87(0.51-1.48)	0.611	1.06(0.76-1.48)	0.748
5	rs2300782	*CAMK4*	T	0.96(0.81-1.12)	0.552	0.91(0.74-1.12)	0.378	0.92(0.80-1.06)	0.236
6	rs17083119	*C6orf170*	G	0.96(0.73-1.26)	0.76	0.96(0.68-1.35)	0.804	1.08(0.87-1.34)	0.471
6	rs7772697	*UST-TAB2*	C	1.04(0.83-1.30)	0.726	0.97(0.74-1.29)	0.856	1.04(0.87-1.25)	0.642
10	rs1571942	*PLXDC2*	C	0.89(0.68-1.15)	0.368	0.76(0.54-1.06)	0.106	0.92(0.74-1.14)	0.456
10	rs12219125	*PLXDC2-NEBL*	T	0.91(0.69-1.18)	0.470	0.78(0.56-1.11)	0.165	0.96(0.77-1.20)	0.714
10	rs4838605	*ARHGAP22*	C	1.09(0.83-1.44)	0.530	1.15(0.82-1.62)	0.434	1.05(0.83-1.32)	0.688
10	rs4462262	*ZWINT-MRPS35P3*	T	1.23(0.86-1.75)	0.255	1.04(0.65-1.67)	0.869	1.11(0.82-1.51)	0.485
11	rs899036	*API5*	C	1.17(0.87-1.57)	0.290	1.45(1.03-2.06)	0.035	1.06(0.83-1.35)	0.658
11	rs10501943	*CNTN5*	C	1.43(0.88-2.33)	0.145	1.67(0.94-2.96)	0.082	1.19(0.79-1.79)	0.403
13	rs9565164	*TBC1D4-COMMD6-UCHL3*	C	0.87(0.73-1.04)	0.135	0.82(0.65-1.03)	0.081	0.93(0.80-1.08)	0.317
13	rs16953072	*HS6ST3*	T	1.03(0.70-1.53)	0.868	1.19(0.75-1.91)	0.463	1.18(0.86-1.61)	0.310
15	rs10519765	*FMN1*	A	0.83(0.63-1.09)	0.170	0.83(0.59-1.16)	0.266	1.03(0.82-1.29)	0.794
16	rs4787008	*RBFOX1*	A	0.40(0.07-2.27)	0.299	0.78(0.13-4.76)	0.788	0.29(0.06-1.30)	0.106
19	**rs2115386**	***INSR***	**G**	**1.31(1.11-1.55)**	**$1.7x10^{-3}$**	**1.47(1.19-1.83)**	**$4.2x10^{-4}$**	1.07(0.93-1.22)	0.367
19	rs10403021	*VSTM2B-POP4*	T	0.978(0.82-1.17)	0.805	0.98(0.78-1.23)	0.847	0.95(0.82-1.11)	0.500

CHR: Chromosome; A1: Minor allele. *Adjusted for age, duration of diabetes, gender, systolic blood pressure, diastolic blood pressure, and HbA1c.

- rs2115386 of *INSR* showed significant associations with STDR ($P_{adjusted} = 1.7x10^{-3}$; OR[95%CI]: 1.31[1.11-1.55]) and PDR ($P_{adjusted} = 4.2x10^{-4}$; OR[95%CI]: 1.47[1.19-1.83]).
- A significant association of an intergenic SNP located between *MYT1L* and *TSSC1* (rs10199521) with PDR ($P_{adjusted}$ = 6.8x10-3; OR[95%CI]: 1.34[1.09-1.67]) was observed.
- An intergenic SNP, rs9866141, located between *KRT18P34* and *VEPH1* was significantly associated with both STDR ($P_{adjusted}$ = 0.010; OR[95%CI]: 1.50[1.10-2.05]) and DN ($P_{adjusted} = 5.4x10^{-4}$; OR[95%CI]: 1.57[1.22-2.02]). Another SNP (rs13064954) in strong linkage disequilibrium (r^2 = 0.875) with rs9866141 also showed a significant association with DN ($P_{adjusted} = 2.5x10^{-3}$; OR[95%CI]: 1.46[1.14-1.86]).

Conclusions

- We have successfully replicated the significant associations of several SNPs identified in previous GWAS with severe retinopathy (STDR and/or PDR) in Chinese diabetic patients.
- We have also demonstrated the significant association of a DR-associated SNP *KRT18P34-VEPH1* rs9866141 with DN, providing supporting evidence for shared common pathogenetic pathways between DR and DN.
- Whether these SNPs can be used for early identification of subjects at high risk of developing microangiopathic diabetic complications warrants further evaluation in prospective studies.

Key references

1. Fu YP *et al.* (2010) J Ophthalmol. pii: 861291.
2. Huang YC *et al.* (2011) Ophthalmology.118(4):642-8.
3. Grassi MA *et al*. (2011) Hum Mol Genet. 15;20(12):2472-81.
4. Sheu WH *et al.* (2013) Hum Mol Genet. 1;22(15):3165-73.

Acknowledgements

- This study was supported by the Seed Funding Programme for Basic Research grant awarded to EYL Hui.