Identification of ANXA2 as a Potential Susceptibility Gene for Diabetic Retinopathy in a Genome-Wide Association Analysis in Chinese Patients With Type 2 Diabetes Mellitus

Chloe YY Cheung, PhD[1], Chi Ho Lee, MBBS[2], Carol HY Fong, MSc[1], Wing-Sun Chow, MD[2], Yu Cho Woo, MD[2], Michele Yuen, MBBS[2], Kathryn CB Tan, MD[2], Aimin Xu, PhD[1], Pak C. Sham, PhD[1], Karen SL Lam, MBBS, MD[1].

[1]The University of Hong Kong, Hong Kong, Hong Kong, [2]The University of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong.

Background: Diabetic retinopathy (DR) is the most frequent microvascular complication of type 2 diabetes mellitus (T2DM). Variation in allele frequencies between different ethnic groups may influence the detectability of the risk variants in different populations. It is therefore important to conduct ethnic-specific association analysis to discover novel loci. The major objective of this study was to conduct a 2-stage genome-wide association study (GWAS) to identify novel susceptibility single nucleotide polymorphisms (SNPs) for sight-threatening DR in Chinese patients with T2DM.

Methods and Materials: The discovery stage consisted of 681 STDR cases and 758 non-STDR controls of Southern Chinese ancestry. The Illumina Infinium Asian Screening Array (ASA) was used for genotyping of the subjects. Imputation was performed using the TOPMed Imputation Server. SNPs with minor allele frequency (MAF) <0.01 and INFO score <0.3 were excluded. Single variant association analysis was performed in SNPTEST using the multiple logistic regression model with adjustment for age, gender, duration of diabetes, hypertension, hemoglobin A1c (HbA1c), and the first five principal components. The replication cohort was comprised of an independent sample set of 278 STDR cases and 834 non-STDR controls. Meta-analysis of the association results of the discovery and replication stages was conducted using the "GWAMA" software. The inverse variance fixed-effect method was used to meta-analyze the summary statistics of the two stages.

Results: In the discovery stage, the strongest association was detected at an intronic variant of *ANXA2* ($P=1.87\times10^{-7}$; OR[95%CI]:1.59[1.31–1.96]). Ninety-three SNPs showing suggestive associations ($P<5\times10^{-5}$) with STDR in the discovery stage were selected for replication. In the meta-analysis of the two stages, the *ANXA2* SNP again showed the strongest association with STDR ($P=2.18\times10^{-6}$; OR[95%CI]: 1.45[1.24–1.70]). *ANXA2* encodes the annexin A2 which has been shown to play an important role in promoting angiogenesis. An intronic SNP of *DOC2B*, a tumor suppressor gene that exhibits functions in cell proliferation and migration, also demonstrated a marginal association with STDR ($P=5.17\times10^{-6}$; OR[95%CI]: 1.41[1.22–1.63]). Two intergenic variants located at the *RPL31P11-FCRLA* ($P=7.25\times10^{-6}$; OR[95%CI]: 1.54[1.27–1.85]) and *COL6A1-COL6A2* ($P=9.60\times10^{-6}$; OR[95%CI]: 0.73[0.63–0.84]) loci also showed suggestive associations with STDR.

Conclusion: Several novel STDR-associated genetic variants were identified in this genome-wide association study. Our findings have shed new lights on the genetic basis of STDR in Chinese patients with T2DM. Further validation in independent cohorts to validate our findings are warranted.

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DIABETES COMPLICATIONS AND COMORBIDITIES

Immune Checkpoint Inhibitor Mediated Insulin Dependent Diabetes: Observations at a Cancer Center

Rebecca Jeun, MD[1], Conor Best, MD[2], Priyanka Iyer, MD[3], Victor Ralph Lavis, MD[4], Jeena Mary Varghese, MD[5], Isabella Glitza Oliva, MD, PhD[6], Ramona Dadu, MD[5], Sonali Thosani, MD[7].

[1]Baylor College of Medicine, Houston, TX, USA, [2]MD Anderson Hospital, Houston, TX, USA, [3]PeaceHealth Medical Group, Eugene, OR, USA, [4]University of TX MD Anderson Cancer Center, Houston, TX, USA, [5]University of Texas MD Anderson Cancer Center, Houston, TX, USA, [6]MD Anderson Cancer Center, Houston, TX, USA, [7]UT-MD Anderson Cancer Center, Houston, TX, USA.

Immune checkpoint inhibitors (ICIs) have rapidly changed the landscape of oncologic care and are now often used in the front line setting for many types of cancers. These agents attempt to harness the immune system to target cancer cells (ICIs) by releasing inhibition of T cell response against tumor cells. With increasing use of ICIs, a new spectrum of immune-related adverse events (irAEs) has emerged including a number of endocrinopathies. A distinct form of ICI-mediated insulin dependent diabetes (ICI-DM) has become increasingly recognized. To better characterize this disease entity and longer-term consequences, we performed a retrospective review of medical records of patients diagnosed with ICI-DM between April 2014 and July 2020 at the MD Anderson Cancer Center. This cohort of 68 patients represent the largest single institution cohort described to date. Baseline characteristics of our cohort are consistent with what has been reported in other case series and meta-analyses with median age at presentation 61 years old (range 32–83 years old), slight male predominance (59% vs 41%), and strong association with anti-programmed cell death protein 1 (anti-PD-1) therapy (59%). Melanoma was the most commonly represented underlying malignancy (29%). The majority of patients (66%) presented with diabetic ketoacidosis. At presentation, median HbA1c was 7.8 % (n < 5.7%) and median C-peptide was 0.2 ng/ml (range <0.1–3.4). Pancreatic autoantibodies were present in 49% of patients. Median insulin dose was 0.54 units per kg per day[T1] (range 0.25 to 1.07 units per kg) at first follow up suggesting these patients may have varying levels of insulin sensitivity[T2]. On most recent follow up at a median[T3] of 40 weeks (range 8 to 261 weeks), median HbA1c was 7.9% and median insulin requirement remained 0.54 units per kg (range 0.14 to 1.2 units per kg). 22% of patients were on insulin pump therapy[T4]. ICI-DM is an irreversible immune-related adverse endocrinopathy characterized by frequent presentation with fulminant hyperglycemia and DKA, persistent beta cell dysfunction necessitating long term insulin therapy and mixed evidence of beta-cell autoimmunity. Median insulin requirement was

more consistent with type 1 diabetes, but a wide range was present. Adequate glycemic control was generally achievable on insulin therapy.

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DIABETES COMPLICATIONS AND COMORBIDITIES

Initial Combination Empagliflozin and Linagliptin Improves Kidney Fibrotic Marker in Patients With Type 2 Diabetes: A Randomized Controlled Trial

Nattapol Sathavarodom, MD, Thanaporn Putthanuparp, MD, Verapon Pinphanichakarn, MD.
Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand.

Background: Transforming growth factor-beta 1 (TGF- ß1) is a novel cytokine marker and also one of the therapeutic targets in the treatment of diabetic kidney disease. Both sodium glucose co-transporter 2 inhibitor and dipeptidyl-peptides 4 inhibitor reduce TGF- ß 1 level in animal studies, but whether it is effective in human is unknown. **Objective:** To evaluate the effects of combinations of empagliflozin/linagliptin, comparing with empagliflozin alone, in patients with type 2 diabetes**. Material and Methods:** Subjects are randomized to a combination of empagliflozin 10 mg and linagliptin 5 mg (n = 23), or empagliflozin 10 mg (n = 22) as add-on to standard treatment for 12 weeks. The primary end point is changed from baseline in serum TGF- ß1 at 12 weeks. **Results:** Among the 45 subjects who completed the study, mean change in TGF-ß1 was -928.2 + 1,204.2 pg/mL, and +206.6 + 592.5 pg/mL in the empagliflozin/linagliptin group and empagliflozin group, respectively (p <0.001). Mean change in estimated glomerular filtration rate (eGFR) increased in the empagliflozin /linagliptin group 4.4 + 7.59 mL/min/1.73m^2, whereas mean eGFR decreased in empagliflozin group -0.06 + 11.16 mL/min/1.73m^2 (p =0.133). Mean change in HbA1c was -1.3 + 0.6% and -0.4 + 0.6% in empagliflozin/linagliptin and empagliflozin group, respectively (p<0.001). Baseline level of eGFR significantly correlated with baseline TGF- ß1 but did not predict response to therapy. **Conclusion:** Initial combination empagliflozin and linagliptin may delay progression of kidney fibrosis as early as 12 weeks of treatment. Our study supports that this combination had synergistic action not only glycemic control but also beneficial in kidney protection. **Keyword:** transforming growth factor - ß1, diabetic kidney disease, combination empagliflozin and linagliptin

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DIABETES COMPLICATIONS AND COMORBIDITIES

Management of Late Dumping Syndrome Induced Hypoglycemia With GLP-1R Agonist

Amna Ali Shaghouli, MD, FRCPC, Razan Ballani, BS, Naglaa Mesbah, BS.
Glycemia Clinic, Kuwait, Kuwait.

Background: Late dumping syndrome is a prominent post-bariatric surgery side effect. Glucose-dependenthyperinsulinemia, induced by elevated gastric inhibitory polypeptide (GIP) and glucagon-likepeptide-1 (GLP-1) levels, leading to 2–3 hours post-prandial hypoglycemia. In literature, several managements are available: dietary changes, glucosidase inhibitor, andsomatostatin analogues. In case of failure of those strategies, partial or total pancreatectomy isindicated. Recently, management using GLP-1R agonists showed promising effect inmanagement of late dumping syndrome induced post-prandial hypoglycemia. (1)AimThe aim of this study was to investigate the effect of using GLP-1R agonists w/o low glycemicindex diet for treating dumping syndromes induced post-prandial hypoglycemia in post bariatricsurgery patients. **Methods:** A sample of 27 cases (25 females, 2 males) mean age 44.64, SD 10.2 of post-bariatric surgerywere managed using GLP-1R w/o low-glycemic index diet after being diagnosed with the latedumping syndrome induced post-prandial hypoglycemia for duration 1–3 years post-surgery. The27 were sent a survey of 13 questions related to their experience pre-and post-management plan. **Results:** Out of the 27 patients, 15 responded to the survey. The results showed 100% of the participantsdeveloped episodes of severe symptomatic late dumping syndrome with hypoglycemiasymptoms diagnosed after one and half years of their symptoms. 87% of them experiencedhypoglycemia post meals 2–3 hours.70 % of the participants got hypoglycemia more than 5episodes per week (less than 4.0 mmol/l) which was confirmed by blood glucose monitoring. After starting treatment with GLP-1R agonists with or without low-glycemic index diet, 87% ofthe participants reported that the hypoglycemia episodes were reduced. Out of those 87%participants 46% did not get any hypoglycemia episode and 54% of them experienced 1–2 timeshypoglycemia episodes. **Conclusion:** The results of the survey showed the successful reduction or prevention of late dumpinghypoglycemia episodes frequency post-bariatric surgery by GLP 1R agonist with or without lowglycemicindex diet. **References:** Non, A.N.H.W.H. and Black, H., 2012. Scope of the Problem. *Am J Prev Med*, *42*, pp.563–70.Chiappetta, S. and Stier, C., 2017. A case report: Liraglutide as a novel treatment option in late dumping syndrome. *Medicine*, *96*(12).

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DIABETES COMPLICATIONS AND COMORBIDITIES

Mild Cognitive Impairment Screening in Older Adults With Type 2 DM

Daniela Victoria Pirela, MD[1], Victor Cevallos, MD[2], Jorge G. Ruiz, MD[2].
[1]MetroHealth Medical Center, Cleveland, OH, USA, [2]Miami VAHS GRECC, Miami, FL, USA.

Introduction: Older adults (O-A), more than 65 years old, are a heterogeneous group of patients in terms of functionality, social support and health status that implies a wide range of co-morbidities including mild cognitive impairment (MCI) and unidentified dementia. De-intensification