Title	Association of the KCNJ11 genetic variant (rs5219) with progression of glycaemia in a 12-year prospective study
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Citation	The 16th Medical Research Conference, The University of Hong Kong, Hong Kong, 22 January 2011. In Hong Kong Medical Journal, 2011, v. 17 suppl. 1, p. 20, abstract no. 22
Issued Date	2011
URL	http://hdl.handle.net/10722/165141
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Using glycosylated haemoglobin to define the metabolic syndrome in adults in the United States

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Introduction: Recently, the American Diabetes Association has proposed the use of glycosylated haemoglobin (GHb) in the definition of diabetes and the category of increased diabetes risk. We therefore investigated whether GHb can be used instead of fasting plasma glucose in identifying individuals with the metabolic syndrome, which is associated with increased risk of cardiovascular diseases.

Methods: Participants of the US National Health and Nutrition Examination Survey (NHANES) 1999-2006 who had fasting blood glucose were included (n=3551 in 1999-2002 and n=3412 in 2003-2006). The metabolic syndrome was defined using International Diabetes Federation criteria in 2009. Raised blood glucose was defined either as fasting glucose ≥100 mg/dL (5.6 mmol/L), or as GHb ≥5.7%.

Results: In 2003-2006, there was 91.3% agreement between GHb and fasting glucose when either is used to define the metabolic syndrome, although the use of GHb slightly lowered the syndrome's prevalence (34.8% vs 38.8%, P=0.012). The agreement was good (≥87%) irrespective of age, sex, race/ethnicity and body mass index. Only 2.3% of the sample population had the metabolic syndrome defined using GHb but not using fasting glucose. The syndrome, defined using GHb alone, was associated with cardiovascular diseases (ischaemic heart disease, heart failure or stroke) [OR=1.95, P=0.002]. Similar results were found in 1999-2002.

Conclusions: Using GHb instead of fasting glucose to define the metabolic syndrome is feasible. The syndrome defined in this way also identifies individuals with increased cardiovascular risk.

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Association of the *KCNJ11* genetic variant (rs5219) with progression of glycaemia in a 12-year prospective study

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Objective: The potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) genetic variant, rs5219, has been found to be associated with type 2 diabetes mellitus (T2DM) in various populations. This project aimed to examine whether this genetic variant could predict the progression of glycaemia in a 12-year prospective study in Southern Chinese.

Methods: We conducted a 12-year prospective study in the population-based Hong Kong Cardiovascular Risk Factors Prevalence Study (CRISPS) cohort. We genotyped rs5219 in 427 subjects who showed progression of glycaemia (NGT→IGT/IFG/T2DM or IGT/IFG→T2DM) from baseline to 12-year follow-up assessment (CRISPS-3) and 901 subjects who were NGT at baseline and remained NGT at CRISPS-3.

Results: We observed significant association of rs5219 with the progression of glycaemia (P=0.004; OR=1.28; 95%CI, 1.08-1.52). Multivariate logistic regression analysis showed that rs5219 was independently associated with the progression of glycaemia, after adjustment for age, sex, body mass index (BMI) and the insulin resistance index HOMA-IR (P=0.027; OR=1.24; 95%CI, 1.03-1.51). Similar findings were obtained if waist circumference was included in the model instead of BMI (P=0.019; OR=1.26; 95%CI, 1.04-1.53). If HOMA-IR was replaced by fasting glucose level or 2-hour post-OGTT glucose level in the model, rs5219 remained a significant independent predictor of glycaemic progression, whether BMI or WC was included in the model.

Conclusions: These results suggested that the *KCNJ11* genetic variant rs5219 may be useful for prediction of the progression of glycaemia in Southern Chinese.

Acknowledgements: This research was supported by a CRCG seeding fund for basic research from the University of Hong Kong to Professor KSL Lam.