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Implication of the type 2 diabetes susceptibility loci identified in genome-wide association studies: long-term follow-up studies in Southern Chinese

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Objective: Genome-wide association (GWA) studies have led to the identification of novel susceptibility loci which showed promising associations with type 2 diabetes (T2DM). This project aimed to establish the role of these novel T2DM-susceptibility loci in Southern Chinese.

Methods: Seventeen T2DM-associated single nucleotide polymorphisms (SNPs) were examined for their associations with glycaemic progression in an 8-year follow-up study based on subjects from the CRISPS cohort. Three SNPs which showed potential associations (P<0.1) with glycaemic progression were further evaluated for associations with T2DM development in a 12-year follow-up study.

Results: In the 8-year follow-up study for glycaemic progression involving 518 glycaemic progression cases and 998 persistent normal glucose tolerance (NGT) controls, the combined genetic risk score of these SNPs showed an odds ratio (OR) of 1.07 ($P=1.3x10^{-3}$) for each additional risk allele. Moreover, the *CDKN2A/B* rs10811661 was significantly associated with glycaemic progression (OR=1.19; P=0.026). Trends for associations with glycaemic progression were also observed in *KCNJ11* rs5219 (OR=1.17; P=0.051) and *IGF2BP2* rs11711477 (OR=1.17; P=0.086). In the 12-year follow-up study for T2DM development involving 200 incident T2DM cases and 903 persistent NGT controls, *CDKN2A/B* rs10811661 showed a significant association with incident T2DM (OR=1.42; $P=2.3x10^{-3}$) which persisted after adjustment for confounding factors.

Conclusions: This study has demonstrated the combined genetic effect of the T2DM-associated SNPs, identified from GWA studies, on glycaemic progression in Southern Chinese. *CDKN2A/B* rs10811661 which showed an independent association with T2DM development warrants further investigation.

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Efficacy and safety of single agent sunitinib in treating advanced hepatocellular carcinoma patients after sorafenib failure: a prospective, open-label, phase II study

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Background: This is an open-label and single-arm phase II study to assess the efficacy and tolerability of sunitinib for the treatment of sorafenib-refractory advanced hepatocellular carcinoma (HCC) patients.

Methods: Between October 2008 and October 2010, eligible patients with advanced HCC and documented disease progression after sorafenib treatment received sunitinib 37.5 mg continuously at Queen Mary Hospital, Hong Kong. Response assessment was performed after every 8 weeks. The primary endpoint was time-to-progression (TTP) and the secondary endpoints were tumour response rate (RR), overall survival (OS), and safety.

Results: At the time of analysis, 38 patients were recruited in the trial. The median age was 56 (range, 27-80) years and all patients were in ECOG Performance Status 0-1. A total of 95% of patients were chronic hepatitis B carriers with underlying Child-Pugh A and B cirrhosis in 70% and 30% of the enrolled patients, respectively. Ten (25%) patients had tumour vascular invasion and 32 (80%) patients had extra-hepatic metastasis. Among 35 evaluable patients, RR was 6% with two patients achieved partial response and another 12 (34%) patients achieved stable disease. Overall, 40% of patients derived clinical benefits from sunitinib treatment for at least 8 weeks. The median TTP was 2.9 (0.5-15) months and OS was 5.2 (1-22.5) months. Malaise (60%), neutropenia (45%), and diarrhoea (36%) were the most commonly encountered adverse events, with nearly 30% of patients experienced grade 3 or 4 toxicity. No treatment-related death was reported.

Conclusions: Sunitinib has substantial anti-tumour activity with manageable toxicity profile in treating sorafenib-refractory advanced HCC population. These data may imply sunitinib inhibits signalling pathways involved in sorafenib resistance and support the hypothesis of sequential use of antiangiogenic tyrosine kinase inhibitors in treating advanced HCC patients.