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Largest east asian genetic study reveals novel diabetes genes

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An international team of researchers aims to identify genetic targets that can enhance precision medicine efforts and treatment of diabetes

In the largest non-European diabetes genetics study to date that involved 433,540 East Asian individuals from China, Hong Kong, Japan, the Philippines, Singapore, South Korea, Taiwan and USA, an international team of 113 investigators co-led by five senior authors, including Dr Xueling Sim from NUS Saw

Swee Hock School of Public Health (NUS SSHSPH) and Dr Karen Mohlke from University of North Carolina, identified 61 new genetic variants associated with Type 2 diabetes (T2D).

Findings include discovery of variants near genes involved in skeletal muscle, and pancreatic functions as well as in alcohol metabolism (e.g. *GDAP1*, *PTF1A*, *SIX3*, *ALDH2),* and also in genes linked to higher levels of fat around the belly in East Asian individuals, e.g. *NID2*. These genes had not been linked with T2D before and may help explain why East Asian individuals get T2D even though they are not obese based on their body mass index (BMI) measurements. The study was published in prestigious scientific journal, *Nature*, on 6 May 2020.

“While a recent study of 900,000 European individuals discovered many new genetic variants linked to T2D, we were still able to make novel findings as we were studying such a large number of East Asian individuals, where these variants are more common. The identified variants are relatively rare in Europeans and thus missed in the European studies,” said Dr Sim. She added, “We learnt over the years that European and East Asian individuals share many T2D genetic variants, but studying East Asian individuals in such an unprecedented collaborative scale allows us to expand the number of genetic variants associated with diabetes. This can help us understand population differences in the development of T2D.”

The researchers made another striking observation: genetic variants can act through multiple close-by genes in different tissues to influence T2D development. For example, one gene may influence the production of insulin in the pancreas, while another gene close by could affect the use of insulin in the muscle.

“These results help further our understanding of the genetic basis for T2D across populations and provide new targets for

T2D drug discovery," said Dr Karen Mohlke of the University of North Carolina, one of the co-senior authors.

"Genetic variants are present in all our genomes, some of which predispose individuals to disease like T2D. Due to differences in population history, some variants are more common in one population than another. This study emphasizes the importance of including large numbers of individuals from different parts of the world in these studies so that we can better understand the cause of diseases. Singapore, with its multi-ethnic populations from different parts of the work, is an ideal environment for studying this," said Professor E Shyong Tai, Senior Consultant from the Division of Endocrinology at the National University Hospital and Professor at the NUS SSHSPH.

These results serve as a valuable public resource for precision medicine efforts in diabetes. The next steps are to identify which genes are altered by the genetic variants and to determine which of these genes may be targeted for new diabetes drugs and treatments.

The large scale study brought together 23 cohort studies from the Asian Genetic Epidemiology Network (AGEN), a consortium with over 10 years of collaborative history. It includes local cohort studies such as the Singapore Population Health Studies (SPHS), the Singapore Chinese Health Studies (SCHS) from NUS SSHSPH, and the Singapore Epidemiology of Eye Diseases (SEED) studies from the Singapore Eye Research Institute (SERI).