Genomic approaches to improve understanding of T2D molecular phenotypes, mechanisms, and development of major complications in diverse populations

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Project outline

Background: Globally type 2 diabetes (T2D) affects >530 million people (including >100 million in China),[1] leading to premature death and development of macro-vascular (e.g. IHD, stroke) and micro-vascular (e.g. nephropathy, retinopathy, neuropathy) complications. T2D is a complex disease, resulting from defects in one or (more often) multiple physiological pathways (e.g. β-cell insufficiency, dysfunctional insulin signalling, fat accumulation, and inflammation).[2] There is evidence that East Asians are more likely to develop insulin resistance-related T2D than Western populations for reasons that are still not properly elucidated. Better characterisation of the T2D disease phenotypes in diverse populations has the potential to improve risk prediction, identification of novel drug targets, and development of precision medicine treatments for specific profiles of T2D patients.

A large number of genetic variants for T2D have now been identified, with heterogeneity between populations of different ancestry, particularly in allele frequency for many signals, suggesting differences in aetiology and/or the proportions of different subtypes. Based on putative genes and predicted functions, these genetic loci can be used to inform molecular phenotyping of T2D. The application of such molecular phenotyping in large prospective biobanks with fully integrated multi-dimensional data (e.g. genetic, multi-omics biomarkers, and disease outcome including T2D complications) offers a unique opportunity to better understand genetic causes of T2D, clarify likely molecular phenotypes, and explore the biological and pathological pathways underlying the development and progression of T2D.[3,4]

Hypothesis: Different genome-based T2D disease phenotypes or clusters may trigger diverse molecular processes that underlie T2D risk and development of major diabetes complications.

Aims: This proposal aims to: 1) categorize genetic loci into clusters representing likely disease mechanistic pathways (e.g. insulin resistance, β-cell dysfunction); 2) examine, compare and validate the associations of cluster-based genetic risk score with diabetes, risk factors, and major complications in the Chinese with the UK population and other East Asian populations; and 3) explore the roles of circulating protein and metabolite biomarkers (and other biomarkers) as mediators in the above associations and in refining the T2D clustering.

Descriptions of the work to be undertaken: This proposal will have four fully integrated work packages (WP). **WP1**: To use the publicly available T2D genetic loci and previous association studies (e.g. results from MAGIC consortium)[5] to generate clusters of T2D patients that likely represent different disease mechanistic pathways. For each cluster, an externally weighted GRS with respect to overall T2D risk will be assessed in the China Kadoorie Biobank (CKB) and UK Biobank (UKB), with further validation, if necessary, in other populations to assess its utility and associations with T2D. **WP2:** To evaluate the relationships of T2D clusters with progression and development of T2D complications in the CKB and UKB individually, and combined where appropriate. **WP3**: To examine i) the associations of T2D clusters with protein and metabolite biomarkers; and ii) the associations of protein and metabolite levels with risk of major diabetes complications. **WP4.** To use the identified phenotypic and molecular features of the T2D clusters to further refine the T2D clustering.

Contributions of Oxford and NNRCO supervisors:

The project will be based at the CKB study group located in the Big Data Institute Building, under the joint supervision of Professor Zhengming Chen (CKB PI) and Dr Joanna Howson in Novo Nordisk Research Centre Oxford. Additional supervisors may be considered depending on the project needs and analytic skills of successful candidate.

References

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Supervisor's recent relevant publications (5 max per supervisor):

Zhengming Chen:

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Joanna Howson:

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3. Surendran P, +200 authors, **Howson JMM**. Discovery of rare variants associated with Blood pressure regulation through meta-analysis of 1.3 million individuals; *Nature Genetics*, 2020, 52:1314-1332
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