GENETICS

Defining genetic risk of T2DM

A large proportion of the genetic risk underlying the development of type 2 diabetes mellitus (T2DM) has yet to be identified. Now, a new study attempts to address this issue. The authors of this paper conducted exome sequencing on a large cohort, which enabled them to identify several rare variants associated with T2DM and to devise a novel method for identifying further risk variants.

The study participants included 20,791 people with T2DM and 24,440 control individuals without T2DM. The participants were asked to self-report their ethnicity, and identified as Hispanic/Latino, European, East Asian, African American or South Asian. According to the researchers, this study is one of the largest of its kind so far. The exome-sequencing analysis identified 6.33 million variants for further analysis. Of these variants, 2.3% were common, 4.2% were low frequency and 93.5% were rare. Next, the researchers tested each variant for its association with T2DM using a single-variant test. Notably, this analysis identified 15 variants that exceeded exome-wide significance for an association with T2DM.

As the single-variant test has limited power to detect rare variants, the researchers devised a new method for analysing variant sets within genes. This method enabled them to consolidate information from several analyses into four results per gene. Using this approach, the researchers identified *MC4R*, *SLC30A8* and *PAM* as important genes for the risk of T2DM; these three genes have also been identified in previous studies of genetic risk of T2DM. The findings emphasise that few novel single-variant associations are likely to be detected from exome sequencing that could not be detected by genome-wide association studies (GWAS). The authors state that in order to decipher the genetics of complex traits such as T2DM, exome sequencing and GWAS have complementary functions. That is, GWAS can be best used for locus discovery and fine mapping, whereas exome sequencing is suited to identifying rare variants in coding alleles. The authors note that much larger samples will be required to identify further rare variants that reach exome-wide significance. "Until sample sizes increase enough to detect gene-level signals from genetics alone, we need to think about exome sequencing as providing information to support experiments, rather than implicating genes all by itself," says author Jason Flannick.

"I think the most important future direction is to try to come up with better methods to use the suggestive signals in our study to support experiments into new T2DM genes or mechanisms," concludes Flannick. "The last section of the paper outlines a 'decision support' framework to do this, but implementing this fully requires more work to combine the genetic associations with other information that we know about genes."

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ORIGINAL ARTICLE Flannick, J. et al. Exome sequencing of 20,791 cases of type 2 diabetes and 24,440 controls. *Nature* <https://doi.org/10.1038/s41586-019-1231-2> (2019)

BONE

A role for autophagy in bone biology

Autophagy, which is a cellular process of macromolecular and organelle recycling, is now known to have an important role in bone biology. However, the exact task of autophagy in different types of bone cell remains unclear. Research by Reuben Kim and colleagues now begins to unravel the function of autophagy processes in bone.

"In our study, we decided to use mice deficient in Beclin1 in osteoclasts (*Becn1* cKO) because Beclin1 is an indispensable protein for autophagy initiation (for example, phagophore formation)," explains Kim. "We wanted to see what happened in the mice when autophagy gets blocked at the early stage during osteoclast differentiation."

First, Kim and colleagues carried out in vitro experiments using primary bone-derived macrophages (BDMs, these cells are precursors of osteoclasts) obtained from mice and autophagy-reporter mouse

macrophage cell lines. "It is well-known that receptor activator of NF- κ B ligand (RANKL) plays a critical role in osteoclast differentiation," says Kim. The researchers saw that RANKL induces autophagy during osteoclast differentiation. Moreover, Beclin1 overexpression increased osteoclast differentiation of reporter cells. Further examination of the function of Beclin1 in vitro revealed that TRAF6-dependent ubiquitination of Beclin1 is crucial for autophagy induction and osteoclast differentiation.

Importantly, *Becn1* cKO mice showed increased cortical bone thickness in the femur but had decreased trabecular bone mass and quality compared with wild-type animals. Moreover, *Becn1* cKO animals had impaired growth plate formation and chondrocyte differentiation. Ex vivo experiments of BDM showed that the bone-resorbing function of osteoclasts is decreased in *Becn1* cKO mice.

DIABETES

Targeting β -cell senescence

Increased age is a risk factor for the development of type 2 diabetes mellitus (T2DM). However, the contribution of β -cell ageing and cellular senescence to the development of T2DM is unclear. Cristina Aguayo-Mazzucato and colleagues now show that β -cell senescence contributes to T2DM and that this process could be targeted with senolytic therapies.

The researchers isolated pancreatic islets from aged male mice and used RNA sequencing to identify a β -cell senescence signature, which was characterized by downregulation of typical β -cell genes and increased expression of non- β -cell genes. Moreover, the senescent β -cells produce and secrete senescent-associated secretory profile (SASP) factors.

Next, insulin resistance was investigated in mice, mice treated with an insulin receptor antagonist (S961)

or mice fed a high-fat diet. In addition, the importance of senescence was tested by deleting $p16^{INK4A}$ -expressing cells (a marker of senescence) in the mouse models or by administering ABT263 (a senolytic drug that specifically kills senescent cells).

"The most significant findings in our mouse models were that insulin resistance increased β -cell ageing and that by specifically removing senescence cells we were able to recover β -cell function and gene identity as well as glucose homeostasis," explains Aguayo-Mazzucato.

The researchers obtained pancreatic islets from human donors of different ages, BMI and T2DM status. "It was striking to see that the same biology was conserved in humans, with β -cell senescence increased in islets from older donors or those with T2DM or a high BMI, and with senescent human β -cells being specifically targeted