Diabetes is a complex metabolic disorder that affects more than 463 million people across the globe. It is strongly related with obesity, age, and sedentary life. In addition, having a family history of diabetes significantly increases the risk, pointing to the critical role of genetic factors.

In the past decades, great effort has been made to discover the genetic causes of this disease. This challenging process consists in the identification of genomic regions associated with diabetes. By analyzing up to a million type 2 diabetes cases and controls, many hundreds of genomic variants have been identified, but for the great majority it is not known how these DNA variants increase diabetes risk.

To tackle this, scientists have joined forces to create a huge database called TIGER (for Translational human pancreatic Islet Genotype tissue-Expression Resource). This is the result of the Horizon 2020 T2DSystems consortium, funded by the European Commission. Miriam Cnop, scientist at the ULB Center for Diabetes Research, Faculty of Medicine, and endocrinologist in the Erasme Hospital of the ULB, coordinated this consortium.

The scientists in the consortium have joined forces to gather genomic data on pancreatic islets. To study diabetes, the most relevant disease-related cells are indeed human pancreatic islets, which are extremely hard to obtain. The procurement of a sufficient number of samples for these analyses constituted one of the main challenges for this type of studies.

In the TIGER resource, genomic and gene expression data on more than 500 human islet samples were brought together. “This study was only possible through international collaboration, which provided access to pancreatic islets and expertise in clinical research, genomics, bioinformatics, cell and molecular biology and statistics.” says Miriam Cnop, one of the senior authors of the study.

TIGER is one of the largest, if not the largest pancreatic islet resources to date, in which 32 novel target genes were identified that may contribute to type 2 diabetes risk. This is the first step towards understanding how each of these genetic variants increases type 2 diabetes risk, to potentially lead to the development of drug targets.

“It has been a fascinating challenge to put all these data together, harmonize them and leverage the great statistical power that such a large sample size can provide”, says Anthony Piron, one of the lead authors of the publication.

Something only possible by using the supercomputing resources at the Barcelona Supercomputing Center. “The amount of data generated is impossible to manage and analyze with a standard computer. Here, we used the most up to date supercomputing technology, without which we would have not been able to
perform these analyses” says David Torrents, one of the senior authors of this study. The study applied several innovative analytic strategies. Ignasi Moran, one of the lead authors and methods developers, says “A large part of this study consisted in developing new statistical methods to analyze differences in gene expression between individuals. This has allowed us to go one step further in the understanding of how genetic variants increase risk for type 2 diabetes”.

The aggregation of these islet genomic, transcriptomic and epigenomic data resulted in a large type 2 diabetes risk database which contains molecular data on risk variants and islet genomic information. Importantly, the investigators have made these data publicly available, and easily accessible to the diabetes research community through the TIGER web portal (tiger.bsc.es) thereby facilitating the access to and interpretation of these research findings. "We are proud that we are now able to share this wealth of data to the scientific community in an easily accessible way for all researchers in the type 2 diabetes field, without the need of computational or bioinformatic expertise", says Lorena Alonso, one of the lead authors and the main developer of the TIGER portal.

This study also reveals the challenges of aggregating data, especially when protocols differ between institutions. “We had to innovate in several ways in order to make the data and the results robust and reproducible despite the heterogeneity of the datasets. We have been lucky to work together with a multidisciplinary team with expertise in genetics, genomics, and bioinformatics. At the end, thanks to the collaborative science, we are very satisfied with the final result” says Josep M Mercader, one of the senior authors of the study. Miriam Cnop concludes: “The TIGER resource sheds light on the molecular mechanisms driving diabetes development and will catalyze the search for therapeutic targets for different types of diabetes”.

Reference:

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