TYPE 2 DIABETES

Several gene variants have been associated with an increased susceptibility to type 2 diabetes. Variants within the *TCF7L2* gene show some of the largest effects. It is likely that additional gene variants for susceptibility to diabetes will be discovered.

Currently, genetic testing for type 2 diabetes susceptibility is not clinically available in Canada. Furthermore, it is not clear whether such test results would provide health benefits for patients with or without type 2 diabetes. In contrast, it is important to recognize rare monogenic forms of diabetes such as MODY (maturity-onset diabetes of the young) as genetic testing is clinically available and the results can influence treatment and prognosis.

WHAT IS TYPE 2 DIABETES?

Type 2 diabetes is also known as adult-onset diabetes or non-insulin dependent diabetes mellitus (NIDDM). It is characterized by hyperglycemia. It can be caused by defective insulin secretion, defective responsiveness to insulin or increased glucose output by the liver. Approximately 90% of individuals with a diagnosis of diabetes have the type 2 form[1]. The worldwide prevalence of type 2 diabetes has been rapidly rising in the past three decades.[1] The age of onset is usually over 40. It is controlled by diet, exercise and, often, oral hypoglycemic drugs or insulin. Risk factors include obesity, age and family history. Uncontrolled/undetected disease can lead to blindness, heart and kidney disease, reduced blood supply to limbs, nerve damage, or stroke. There is evidence of a genetic component to the risk of type 2 diabetes, including a sibling risk ratio of about 2-4 fold[2].

There are several gene variants associated with an increased susceptibility to type 2 diabetes[2]. Each gene variant contributes a modest effect[2]. Variants within the *TCF7L2* gene show some of the largest effects compared to other susceptibility gene variants[3].

RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION[4,5]

Most of the time, a diagnosis or family history of type 2 diabetes is <u>not</u> a strong indication for a referral for genetic counselling. Patients may prefer a conversation with their healthcare provider about their empiric risks of developing this disease as genetic testing for type 2 diabetes susceptibility gene variants is not currently available in Canadian Genetic Clinics and is not recommended for risk assessment at this time because the presence of these variants is neither necessary nor sufficient for development of type 2 diabetes.

Although uncommon, attention should be paid to individuals where there is:

- Young age at onset (i.e. neonatal period to age 25) of diabetes, with features atypical for type 1 or 2
- The presence of other medical conditions that, in conjunction with the diabetes, suggest a genetic syndrome (e.g. lipodystrophy)

These rare forms of diabetes can be caused by a single gene mutation (i.e. they are monogenic) and, in these cases, genetic counselling and/or genetic testing may be appropriate and may influence treatment and prognosis.

WHAT DOES THE GENETIC TEST RESULT MEAN?

Currently standard clinical genetic testing is not available. Looking at an example of a susceptibility gene, a 2013 meta-analysis that pooled all available data of genetic studies on the variant rs12255372 in the *TCF7L2* gene and type 2 diabetes confirmed that this variant was significantly associated with susceptibility to type 2 diabetes in the global population. The risk allele and the genotypes could increase the risk of type 2 diabetes from 1.363-1.933 fold.[3]

HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?

Not applicable: Testing for the type 2 diabetes susceptibility gene variants is not currently offered as a standard clinical test. As more and more gene variants are identified, clinical testing may be developed.

ARE THERE HARMS OR LIMITATIONS OF GENETIC TESTING?

When such susceptibility testing is available, patients with a low susceptibility risk may have a false sense of reassurance that they will never develop type 2 diabetes. A positive result does not guarantee an eventual diagnosis of type 2 diabetes and might lead to increased anxiety.

See www.gecko-cegco.ca for how to connect to your local genetics centre.

References

[1] Chen, L *et al.* The worldwide epidemiology of type 2 diabetes mellitus-present and future perspectives. *Nat Rev Endocrinol* 2012;8:228-236

[2] Kwak SH, Park KS. Genetics of type 2 diabetes and potential clinical implications. *Arch Pharm Res* 2013;36:167-177

[3] Wang, J. *et al.* Association of rs12255372 in the *TCF7L2* gene with type 2 diabetes mellitus: a meta-analysis. *Braz J Med Biol Res* 2013;46(4):382-93

[4] McCarthy MI, Hattersley AT. Learning from molecular genetics. Novel insights arising from the definition of genes for monogenic and type 2 diabetes. *Diabetes* 2008;57:2889-2898

[5] Malecki MT *et al.* Can geneticists help clinicians to understand and treat non-autoimmune diabetes? *Diabetes Research and Clinical Practice* 2008;82 Suppl2:S83-93

Other type 2 diabetes resources:

www.diabetes.ca (Canadian Diabetes Association)

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Updated from the original Gene Messenger developed for the GenetiKit research project.
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