Topic: Type 2 Diabetes

Summary: 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.

Bottom line: 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.

The Disease
- 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.
- The worldwide prevalence of type 2 diabetes is approximately 6%.
- The prevalence is highest in older groups (e.g. for diabetes, type unspecified, the risk is 10.8% in the 40-59 age group and 23.1% in the >60 age group). Source: 2003-06 US National Health and Nutrition Examination Survey estimates of total prevalence (both diagnosed and undiagnosed) projected to year 2007.
- 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 ~3.5.

The Genes
- There are several gene variants associated with an increased susceptibility to type 2 diabetes.
- Each gene variant contributes a modest effect.
- Most of the gene variants found to date surprisingly influence beta-cell insulin secretion rather than insulin action.
- To date, variants within the TCF7L2 gene show some of the largest effects compared to other susceptibility gene variants.

Consequences of having susceptibility variant allele(s) using TCF7L2 as an example
- Compared with non-carriers, the relative risk of type 2 diabetes in individuals who have two copies of (are homozygous for) the TCF7L2 variant is 2.41. About 7% of the population is homozygous for this variant.
Compared with non-carriers, the relative risk of type 2 diabetes in individuals who have one copy of (are heterozygous for) the TCF7L2 variant is 1.45. About 38% of the population is heterozygous for this variant.

**Who should be offered referral for genetic counselling/testing?**
- Most of the time, a diagnosis or family history of type 2 diabetes is not a strong indication for a referral for genetic counselling. Patients may prefer a conversation with their health care 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.
- Although uncommon, please be on the look out for:
  - Young age of onset of diabetes (i.e., neonatal period to age 25).
  - The presence of other medical conditions in a patient 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., monogenic) and in these cases, genetic counselling and/or genetic testing may be appropriate as it can influence treatment and prognosis.

**Testing for type 2 diabetes susceptibility gene variants**
- Testing for known susceptibility gene variants is not recommended for type 2 diabetes risk assessment at this time because the presence of these variants is neither necessary nor sufficient for development of type 2 diabetes.
- There are rare monogenic forms of diabetes for which gene testing is available and tips to identify these patients are listed above.

**Benefits of genetic testing**
- Not applicable, as 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 become available in the future.

**Harms/limitations of genetic testing**
- Not applicable, as testing for the type 2 diabetes susceptibility gene variants is not currently offered as a standard clinical test.
- However, if clinical testing becomes available in the future, patients with a low susceptibility risk may have a false sense of reassurance that they will never develop type 2 diabetes. Conversely, a positive result would not guarantee an eventual diagnosis of type 2 diabetes and may lead to increased anxiety.

Web Resources: Canadian Diabetes Association (www.diabetes.ca/)

References:
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