Altered DNA Methylation in Patients with Youth Onset Type 2 Diabetes in the iCARE Cohort

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INTRODUCTION

Youth-onset type 2 diabetes is an increasing burden for youth in Canada. Type 2 diabetes in youth manifests similar to type 2 diabetes in adults with more persistent insulin insensitivity and a faster decline in ß cell function.

Compared to adult-onset type 2 diabetes and type 1 diabetes, youth with type 2 diabetes develop micro- and macrovascular complications much earlier in the disease process.

Understanding the pathophysiology of youth-onset type 2 diabetes is crucial for identifying treatment targets and guiding prevention strategies.

Here, we aim to characterize the DNA methylation patterns associated with youth-onset type 2 diabetes.

MATERIALS

iCARE cohort

A prospective observational cohort study of youth diagnosed with type 2 diabetes prior to 18 years of age. Largest cohort of youth with type 2 diabetes covering diverse geographic and ethnic background in Canada.

METHODS

- DNA methylation of whole blood tissue from 306 youths was measured using Illumina **Infinium MethylationEPIC BeadChip**
- Cross-reactive, SNP-affected, and probes in sex chromosomes were filtered out
- R package ***limma*** was used to fit 704 709 remaining probes into a linear regression model accounting for the following covariates: Age, Sex, Smoking, BMI, Genetic Ancestry, Cell-type proportions, and Batch effects.
- Significant results were cross-checked on EWAS atlas for previous association to type 2 diabetes

RESULTS

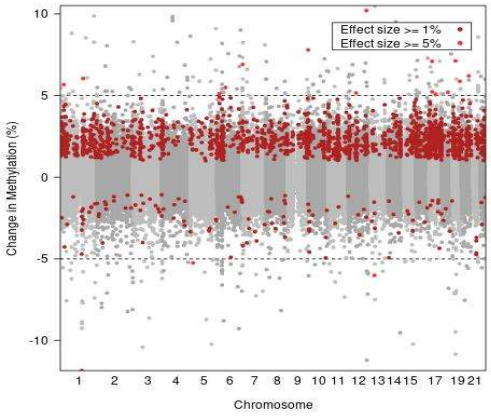
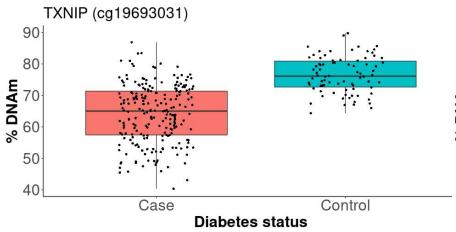


Figure 1. Chicago plot summarizing results for epigenome-wide analyses of associations between childhood-onset type 2 diabetes and blood DNA methylation. 18 CpG sites were found associated to childhood-onset type 2 diabetes (adjusted p-value < 0.05 and effect size > 5). 3 of the 18 CpGs were previously associated with adult-onset type 2 diabetes. 1 864 CpG sites were found to be weakly associated to childhood-onset type 2 diabetes (adjusted p-value < 0.05 and effect > 0.01). .

RESULTS



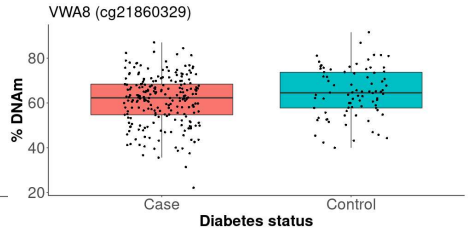


Figure 2. Box plot of DNA methylation levels at cg19693031 (TXNIP) in youth with and without type 2 diabetes. DNA methylation at TXNIP was 12% lower in youth with type 2 diabetes. We also see an increase in variance and distribution of methylation levels at this CpG in youth with type 2 diabetes. These same differences have been found in adult-onset type 2 diabetes. TXNIP is induced by glucose and plays a role in insulin inhibition.

Figure 3. Box plot of DNA methylation levels at cg21860329 (VWA8) in youth with and without type 2 diabetes. DNA methylation at VWA8 was 6% lower in youth with type 2 diabetes. Previous epigenome-wide association studies in adult-onset type 2 diabetes have not identified this CpG. VWA8 is a poorly characterized protein that is known to localize to the mitochondrial matrix.

CONCLUSION

Youth-onset type 2 diabetes is an aggressive form of diabetes that reacts poorly to current treatment and is associated with early development of diabetes complications. We have identified a DNA methylation profile for youth-onset type 2 diabetes in a geographically and ethnically diverse cohort across Canada. Majority of the profile we have identified was not previously found in adult-onset type 2 diabetes. This DNA methylation profile builds the basis for future studies to identify pathways involved in youth-onset type 2 diabetes and test utility of these CpGs for risk stratification and guided treatment.

Future Directions

- Validate this DNA methylation profile in an independent cohort of youth-onset type 2 diabetes
- Identify protective environmental factors that have the opposite effect of youth-onset type 2 diabetes on DNA methylation for preventative strategies

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