Functional effects of TCF7L2 variation in Beta, Alpha and Liver cell lines

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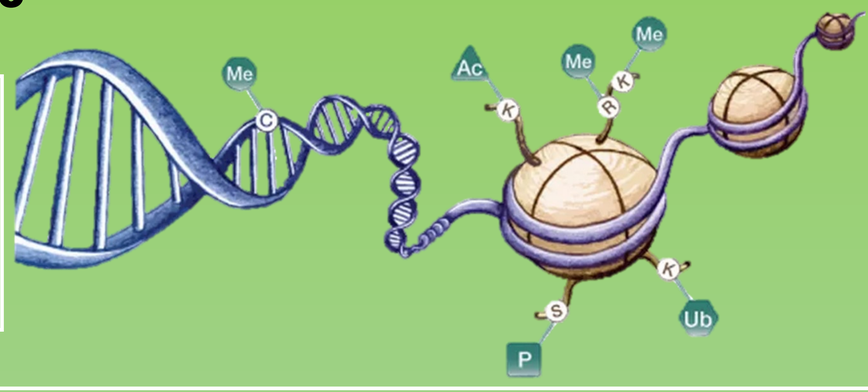
Abstract and main goals:

Diabetes is a metabolic disease that has a multifactorial pathogenesis. Genetic predisposition for Type 2 Diabetes has been long studied and associations have been stablished, yet no exact effect has been detected. TCF7L2 has the higher association to Diabetes. Luciferase Assays were performed in Beta, Alpha and Liver cells to identify the effect of the risk allele on the enhancer activity related to TCF7L2. The results reported lower enhancer activity on the cells that had the alternate allele in comparison to the reference allele. This sets the road to more research on pharmacogenetics.



Background:

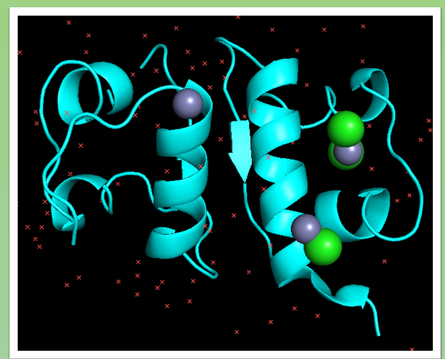
Diabetes is characterized by an abnormal high blood sugar levels (or hyperglycemia) and low or elevated levels of insulin. Type 2 Diabetes represents 95% of the total cases of Diabetes, usually presents itself in middle or later years of life.

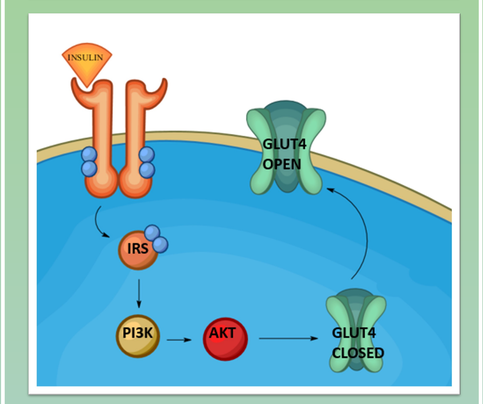
Pancreatic islets are constructed of, mainly, Beta-cells and Alpha-cells, among others. Beta-cells produce insulin, the main protein involved in glucose regulation by activating a signaling cascade that ultimately places GLUT4 transporters on the cell membrane allowing glucose to move from the blood into the cell. Alpha cells participate in glucose regulation by the secretion of glucagon; this hormone elevates glycemia by allowing the release of glucose from cells into the blood.

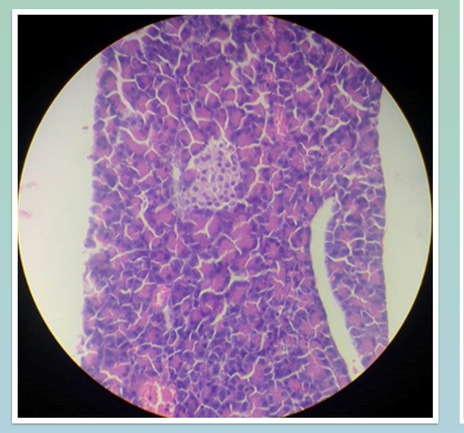
There have been several studies on the genetic risk factor for diabetes, the genes identified are still under review for their exact function on the pathophysiology of the disease. Some of the most talked about are the HLA genes, which have a high rate of variance; TCF7L2 and NKX6.3.

TCF7L2 gene codes for a transcription factors involved in the WNT signaling pathway, important in cell development and growth. It's SNP's rs7903146 has been associated with impaired insulin secretion and Diabetes.

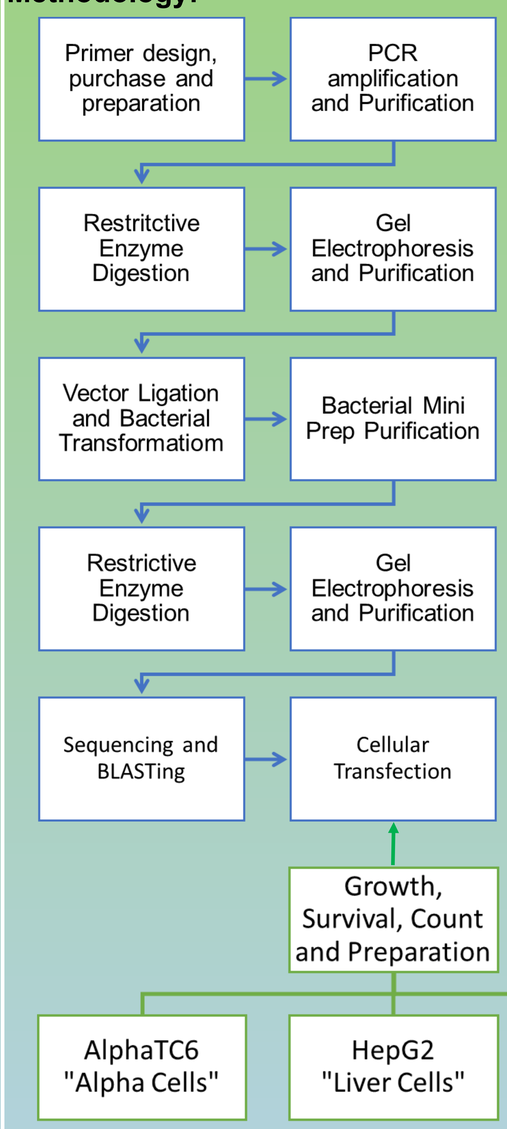
Diabetes is known to be a multifactorial disease. Both genetic and environmental factor are to be considered in the pathogenesis. Epigenetics, defined as non-DNA molecules that can be passed down to future generations and that affects chromatin accessibility, transcription binding and gene promotion.

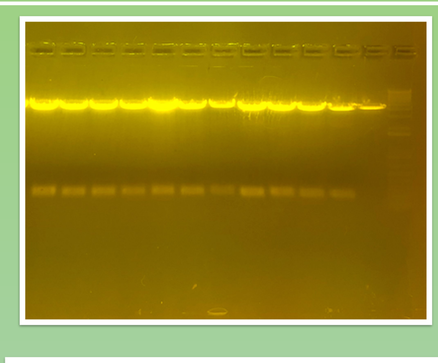


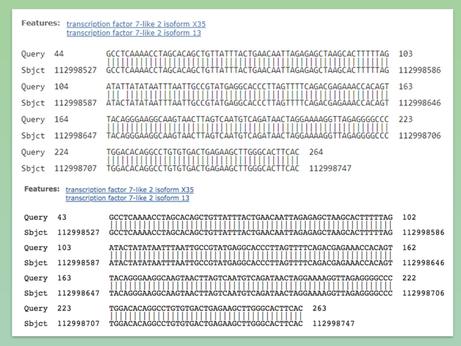




Methodology:

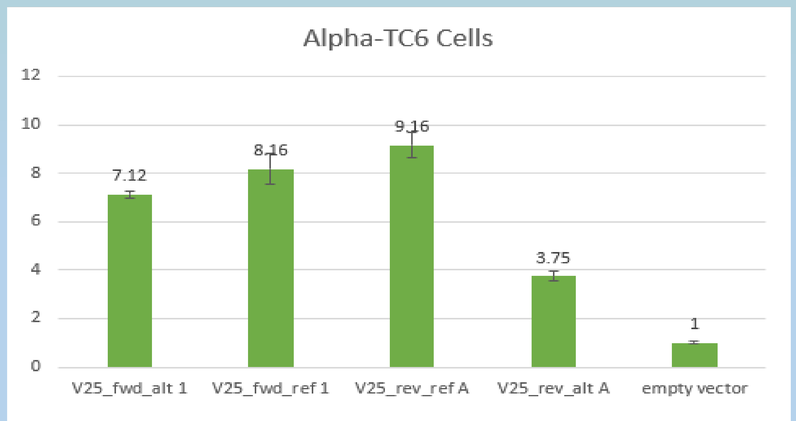


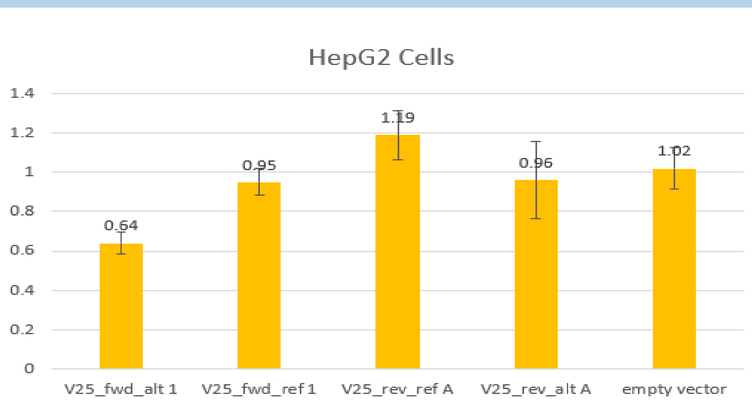


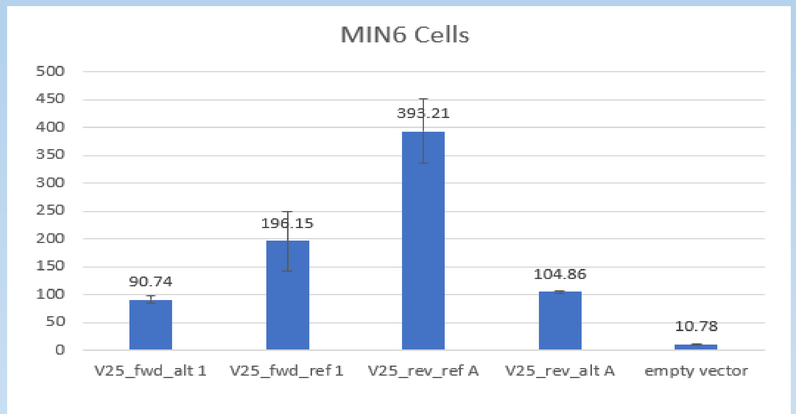


Results:

The luciferase assay reported distinct values for the different alleles in both Firefly and Renilla. The alternate allele showed lower activity in comparison to the reference allele. This could be indicative that the enhancer activity on the alternate allele is reduced and therefore affects gene expression by lowering transcription factor binding and gene expression. It is also worth mentioning that this results were consistent through out the three cell lines and had a major effect on the cell lines that constitute pancreatic islets.







Conclusions and future work:

TCF7L2 variations are a known risk factors for developing Type 2 Diabetes, this project allowed us to understand how the risk alleles had an effect on the enhancer activity by reducing it, . This gives insight into the molecular action of said variation and how it can predispose to Diabetes.

Future work should aim to establish the complete action pathway of this variation and place the road for pharmaceutical therapies to correct this effect. Also performing the Luciferase Assay on other type of cells, like Delta, Ductal, adipose and muscular cells to identify any effect on other glucose relevant tissue as well as ChIP-seq tests.

References:

1.Type 2 Diabetes (2018) Genetics Home Reference for the National Institutes of Health, URL: https://ghr.nlm.nih.gov/condition/type-2-diabetes#genes

2.Gloyn, A; Braun, M & Rorsman, P. (2009) Type 2 Diabetes Susceptibility Gene TCF7L2 and Its Role in β-Cell Function. *American Diabetes Association*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2661580/. 58(4): 800–802.

3.Harvey, R. & Ferrier, D.. (2011). Biochemistry. Baltimore: Lippincott.