

## ABSTRACT SUBMISSION FORM

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# SEX + GENDER

Exploring the role of sex and gender on health research



## CHR D 2020: Abstract Submission Form

### Submitter Name

Manuel Sebastian

### Email

sebasti1@myumanitoba.ca

### Title

The HNF-1a G319S gene variant affects liver metabolism and endogenous glucose production which contributes to early onset Type 2 Diabetes

### Background

Youth-onset Type 2 diabetes (T2D) in the First Nations Anishininiwuk (Oji-Cree) of central Canada are among the highest in the world, and a genetic variant in the hepatic nuclear factor-1a (HNF-1a) gene, known as HNF-1a G319S, strongly associates with T2D in this population. HNF-1a is known to play an important role in the liver, and the liver plays a central role in controlling glucose homeostasis; however, it is unclear how the G319S variant influences liver function.

### Objective

We hypothesized that the G319S variant promotes greater hepatic glucose production and triglyceride storage, which historically may have conferred an adaptive advantage to longer periods of fasting or prolonged periods without carbohydrate intake; however, post-colonization, promotes hyperglycaemia and T2D.

### Methods

CRISPR/Cas9 gene editing was used to knock-in the HNF-1a G319S G>A single nucleotide substitution into C57BL6 mice. G/G (wild type), G/S (heterozygous) and S/S (homozygous) male and female mice were fed a standard chow diet, sacrificed at 6 months of age, and liver tissues collected for gene expression, triglyceride content and glycogen content measurements. Additionally, pyruvate tolerance tests were performed to assess endogenous hepatic glucose production capacity.

### Results

Lipogenic genes such as PPAR-gamma were elevated, and key lipolytic genes such as PPAR-alpha were down regulated in S/S mice; however, no differences in steatosis, liver triglyceride or glycogen content were seen across the three genotypes. Additionally, female S/S displayed elevated endogenous glucose

production during a pyruvate tolerance test.

**Conclusion**

The HNF-1a G319S variant appears to trigger a shift in liver metabolism towards increased lipid synthesis, but not storage, and increased endogenous glucose production, at least in females on a chow diet. This could provide important advantages during long-term fasting, which we are in the process of investigating in this model

**Theme:**

Basic Science

**Do you have a table/figure to upload?**

No

**Are you willing to participate in Goodbear's Den?**

No

**Presenter Status:**

Masters Student

**What was your role in the project?**

All of the above

**Authors**

<b>Name</b>	<b>Email</b>	<b>Role</b>	<b>Profession</b>
Manuel Sebastian	sebasti1@myumanitoba.ca	Presenting Author	Graduate
Taylor Morriseau	morriset@myumanitoba.ca	Co Author	Graduate
Christine Doucette	CDoucette@chrim.ca	Co Author	Assitant Professor