Investigation of the Genetics of Obesity through Single Nucleotide Polymorphisms of the Glucocorticoid Pathway

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Abstract

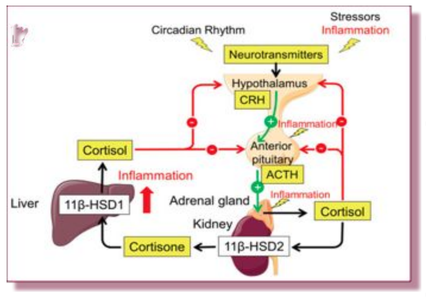
The stress hormone cortisol is responsible for aspects of metabolism and visceral fat formation that are hypothesized to be linked to obesity. Cortisol directly and indirectly influences metabolism by stimulating lipolysis as well as gluconeogenesis, the breakdown of fat and creation of glucose respectively. By interacting with abdominal organs such as the liver and pancreas, cortisol also increases metabolism through downstream hormones, such as glucagon and epinephrine. Cortisol intersects a variety of pathways that influence the breakdown of sugar, making it an important target for metabolic studies.

This study investigates the correlation of mutations in proteins responsible for cortisol action in target tissues, individually and collectively, to clinical measurements of patients with obesity who are seeking or have already sought out bariatric surgery. DNA samples and clinical information were collected from patients of the Ellis Hospital Bariatric Care who were recruited for the study under the supervision of the Ellis Hospital Institutional Review Board. Genotyping of patient samples was done by performing allele specific-polymerase chain reactions (AS_PCR) which were then analyzed through agarose gel electrophoresis to look for single nucleotide polymorphisms (SNPs).

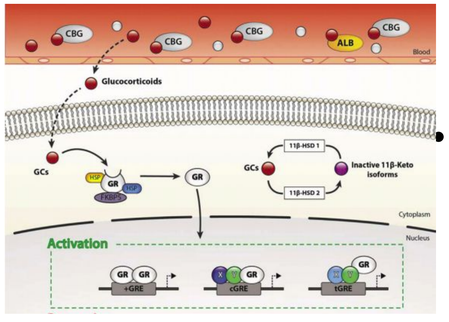
It was found that the mutations throughout the glucocorticoid pathway are present at comparable rates in both the bariatric population and general population except for three SNPs, BclI, TthiII, and N363. Therefore, it can be concluded that there is an increase of mutations in the study population compared to the values for the general public found in literature for increased sensitivity to cortisol.

There are strong correlations between a mutation in the glucocorticoid receptor (GR) and excess body weight. This mutation causes conversion of an aspartic acid to a serine (N363S) in the protein sequence which has previously been shown to cause increased sensitivity to cortisol. As more SNPs are analyzed in combination with each other, more conclusions may be drawn between SNPs and physiological parameters of the patients. High correlations may provide evidence that select bariatric surgeries may be more effective in patients with specific genotypes. If this is the case, bariatric surgery can adopt precision medicine that caters treatment to the patient.

Introduction



- Cortisol, a glucocorticoid hormone, is the primary steroid involved in response to stress
- In its cellular pathway, cortisol binds to the glucocorticoid receptor (GR), which in turn, activates a signaling cascade that results in modification of gene transcription
- High cortisol sensitivity → metabolic syndrome, similar symptoms as Cushing's disease
  - Obesity (higher BMI)
  - Depression
- Mutant genotypes in these target SNPs result in high cortisol sensitivity through the GR, MR, or HSD, and consequently, metabolic syndrome



Glucocorticoids: Cortisol and Cortisone → workhorses of human stress response

Low Cortisol ⟷ **High Cortisol**

Cortisol, Stress and Depression

Hypothalamic Pituitary Adrenal Axis

- Hypocortisolemia
- Metabolic syndrome
- Addisons' Disease

- Hypercortisolemia
- Major Depressive Disorder
- PTSD

Hypothesis

A population of bariatric patients does not have the same allelic frequency of the specified polymorphisms as that of the general population. If there are significant differences in allelic frequency in the bariatric population, there will be a correlation between the single nucleotide polymorphisms and characteristics of obesity along with the efficacy of distinct bariatric treatments.

Methods

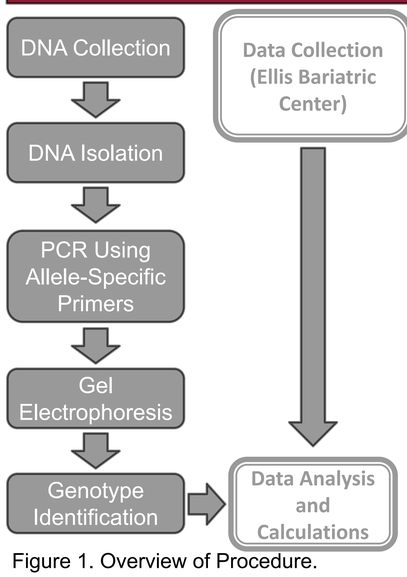


Figure 1. Overview of Procedure.

Table 1: SNPs associated with the GR gene and other cortisol-related genes investigated in this study

Gene	SNPs	Phenotype
Glucocorticoid Receptor	rs41423247 **(BCLI)**	*Hypersensitivity*
	rs56149945 **(N363)**	*Hypersensitivity*
	rs10052957 **(TthIII)**	*Resistant*
Mineralocorticoid Receptor	rs2070951 **(RS207)**	*Hypersensitivity*
	rs846910 **(RS84)**	*Resistant*
11 beta-Hydroxysteroid - dehydrogenase, Type I	rs846910 **(RS120)**	*Hypersensitivity*
	rs5522 **(RS55)**	*Resistant*

Results

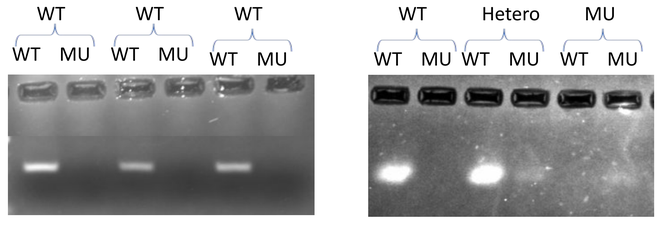


Figure 2. Tthiii PCR 02/19/2021 (left) 04/12/2021 (right). Agarose gel electrophoresis. 1KB ladder. The above bands determine the genotype of the designated samples. Samples with bands at wild type and mutant marks are heterozygous. The samples with bands only in wild type or mutant lanes are the respective genotypes.

Table 1. P-values of BMI association with SNPs in Bcl1, N363, and TthIIIi.

	Bcl1	N363	TthIIIi
Excess Body Weight	0.494	0.0008	0.662
Percent Excess Body Weight Lost	0.113	0.514	0.162

These values demonstrate the lack of statistical significance of the SNPs studied to BMI. T-tests were performed between the average BMI of each genotype.

Pooled t-test, mutant has higher excess body weight for N363.

Results

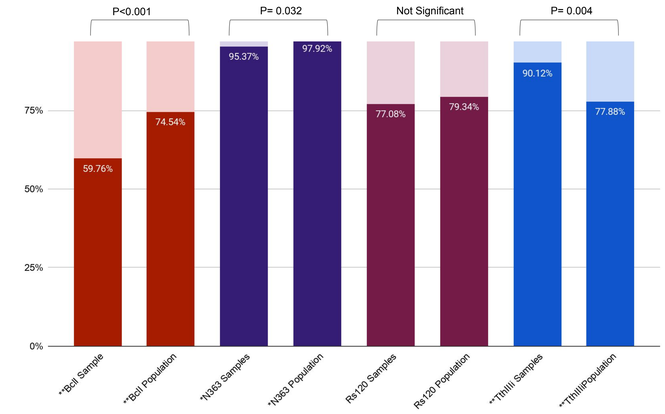


Figure 2. Allelic Frequency of Single Nucleotide Polymorphisms of Bariatric Sample Population Compared to General Population values from literature. This graph displays the accepted allelic frequency from literature to the collected samples through a chi square goodness of fit test, the statistical significance of the allelic frequencies in the bariatric population was determined. At a p<0.05 significance level, Bcl1, TthIIIi and N363 are significantly different than the general population.

** = statistically significant at 99% confidence level
* = statistically significant at 95% confidence level

Conclusions

- N363 has statistical significance to excess body weight
  - People with the N363 mutation have higher weights before bariatric surgery
- Bcll, N363, and TthIIIi are different in the bariatric population in comparison to the general population
  - There is increased sensitivity to cortisol in people with obesity
  - There are genotypic correlations to the bariatric phenotype

Future Directions

- Greater number of samples to determine further statistical significance
- Analyze previous samples' current phenotypic status with more recent data
- Find new SNPs within the cortisol pathway to study
- Expand SNPs beyond just cortisol pathway
- Role of sex in phenotype and genotype
- Acquire lipid profile, blood sugar, and blood pressure

References and Acknowledgements

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