Cortisol Receptor Sensitivity as a Risk Factor for Depression

By

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Introduction

The World Health Organization recently reported the staggering statistic that around 280 million people across the world suffer from depression (1). Depression may manifest in prolonged periods of melancholia and low spirits, absence of motivation or joy in everyday activities, helplessness, isolation, sleep imbalances and is often accompanied by anxiety; all of which can have a negative impact on an individual's quality of life (2). Like many psychological disorders, there are environmental and situational sources for depression such as experiencing a traumatic event or undergoing serious physical health issues (2). However, despite this disorder impacting a substantial portion of the global population, the biological basis and potential risk factors for depression are not yet entirely understood.

Imbalances in chemical messengers in the central nervous system, specifically in the brain, have been linked to depression, among other psychiatric and mood disorders (3). Variations in the activity of the neurotransmitters dopamine, norepinephrine, and serotonin have been found to be associated with depression (3). Dopamine acts throughout the nervous system to modulate emotion, cognition, as well as motor activity; research suggests dysregulation of dopamine synthesis and transmission may contribute to psychopathology such as depression (4). Treatment methods for depression have been established which modulate neurotransmitter activity. Such drugs, like selective serotonin reuptake inhibitors (SSRI) or serotonin–norepinephrine reuptake inhibitors (SNRI), block the reuptake of neurotransmitters so that their effects on increasing mood and emotion are prolonged (5). While these have been employed as treatment methods for depression, these drugs may not address the entire physiological causes of underlying chemical imbalances relating to depression (6).

In addition to neurotransmitters, other chemical messengers called hormones play a role in depression and psychiatric disorders (7). Studies have established links between imbalances in hormones involved in the body's stress response and depressive disorders, providing further insight into the biological workings of depression (7). When a stimulus triggers the stress response, it sets off a hormone-releasing pathway which causes the body to gear up for a response commonly known as the fight or flight response. However, an imbalance in such hormones enables the possibility for an overactive stress response pathway which can facilitate depressive symptoms (8, 9).

Cortisol is a principal stress hormone which mediates the stress response (8). In addition to decreasing glucose metabolism and increasing blood pressure, cortisol stimulates the release of neurotransmitters epinephrine and norepinephrine which act as part of the sympathetic nervous system which prepares the body's autonomic response to stress-inducing stimuli, as visible in Figure 1 (8).

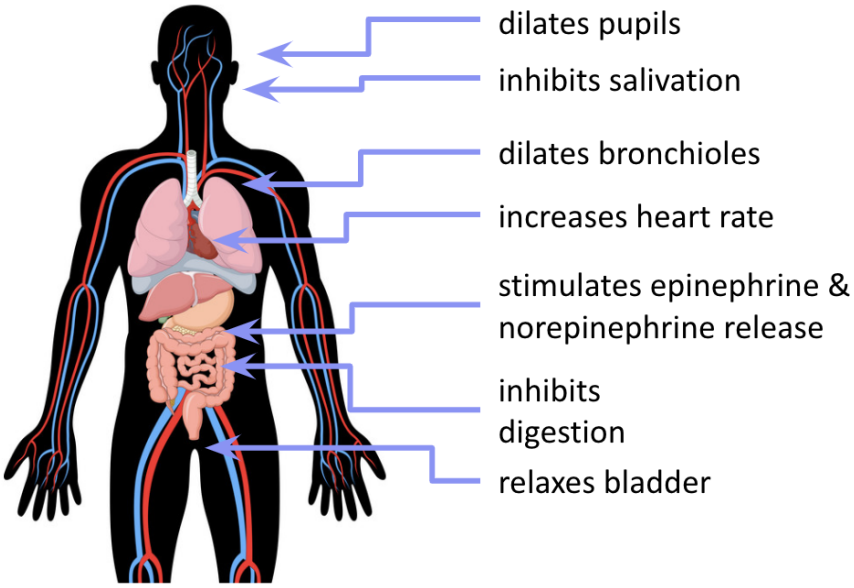

Figure 1. Sympathetic nervous system effects present throughout the body.

Cortisol activity in the body is regulated in multiple ways: centrally and locally. Central regulation of cortisol occurs with the hormonal pathway associated with stress known as the Hypothalamic-Pituitary-Adrenal (HPA) Axis (8). The HPA axis is a series of glands which each release a certain hormone that stimulates the following gland, as seen in Figure 2. Signals from the thalamus and other regions of the brain stimulate the hypothalamus to release corticotropin releasing hormone (CRH) which stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) which then triggers the adrenal gland to release the hormone cortisol. In the HPA axis, cortisol exerts negative feedback which can hinder the stimulation of the hypothalamus and the pituitary to decrease consequently cortisol synthesis and lower cortisol levels in the body (10).

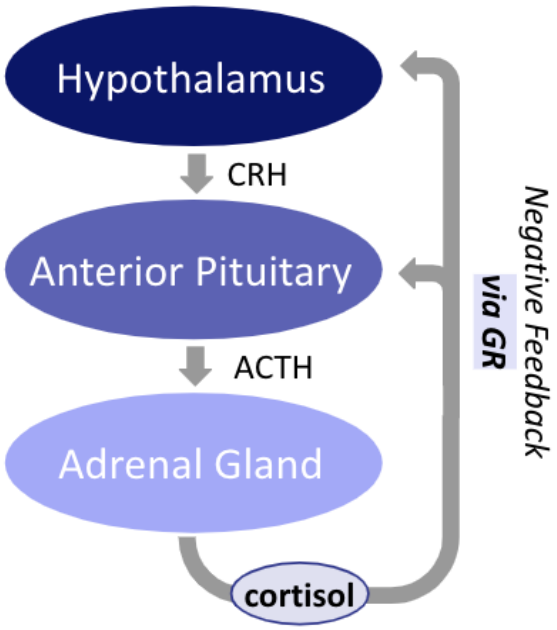

Figure 2. Diagram representing the HPA axis and negative feedback loop regulating cortisol levels.

Local, or peripheral regulation of cortisol is modulated by two enzymes at certain areas throughout the body (8). As seen in Figure 3, peripheral regulation of cortisol alters cortisol to or from its inactive form, cortisone. Two enzymes control this regulation: 11-beta Hydroxysteroid

Dehydrogenase Type 1 (11βHSD1) activates cortisol from cortisone while 11-beta Hydroxysteroid Dehydrogenase Type 2 (11βHSD2) inactivates cortisol to cortisone.

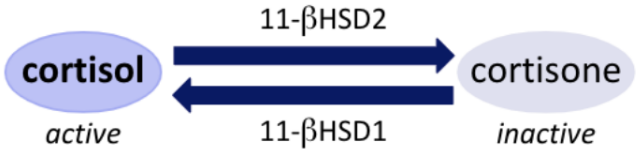

Figure 3. Diagram representing the peripheral regulation of cortisol to or from cortisone.

A mendelian randomized analysis study by Zhou and Qiao found that heightened cortisol levels were associated with a greater likelihood for depression, suggesting that cortisol may contribute in some facet to psychiatric disorders such as depression (4). Studies have also demonstrated that endocrine disorders related to imbalances in cortisol levels are also linked with depressive symptoms (11). Cushing's Syndrome, for example, is a endocrine disorder based on heightened cortisol levels (hypercortisolism) in the body which facilitates increased appetite, especially for high-energy carbohydrates, and contributes to obesity and many adverse metabolic comorbidities (12). Conversely, the endocrine disorder Addison's Disease is linked to deficient cortisol levels (hypocortisolism) which manifests in appetite loss, weight loss, and chronic fatigue (13). While depressive symptoms and psychological comorbidities can result from these metabolic disorders, not all patients with imbalances in cortisol levels have the symptomology of depression, as represented in Figure 4. According to a study by Sonino et al., major depressive disorder symptomology was prevalent in around 50-65% of patients with Cushing's Syndrome (14). A similar frequency of depressive symptoms is found in Addison's Disease (15).

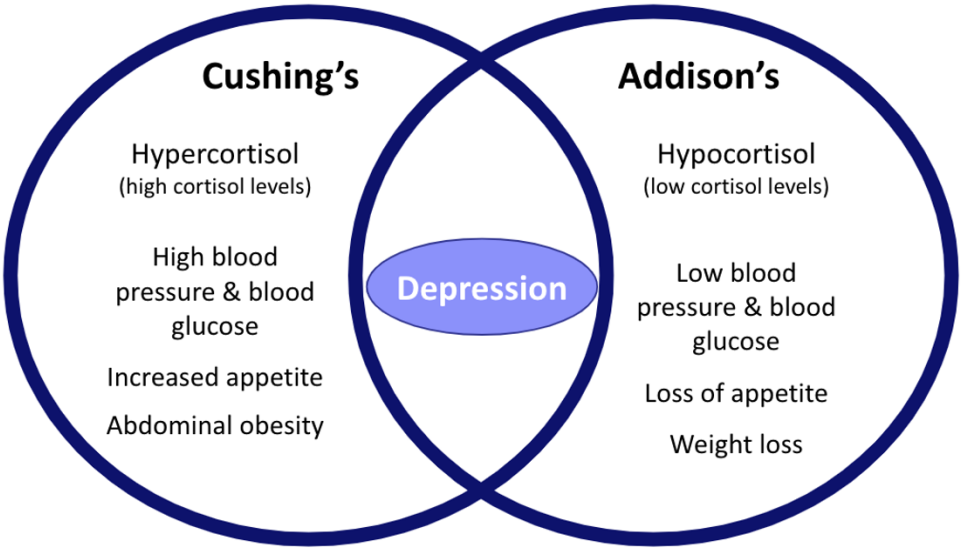

Figure 4. A diagram of the symptoms of metabolic disorders related to imbalances in cortisol levels. Depression is an overlapping symptom relating to imbalances in cortisol levels which only occurs in a portion of patients with these metabolic disorders.

Nevertheless, this does not exclude cortisol entirely as a contributing source of depression. A body of research has indicated studying imbalances in cortisol-receptor sensitivity could lead to a better understanding of the biological mechanisms involved in depression (16; 17). Hormone receptor sensitivity is the receptor's responsiveness to its hormone: a hypersensitive receptor is very responsive to binding its hormone, while a resistant receptor is not very responsive to binding (8). After being produced via the HPA axis, cortisol, like all hormones, is transported throughout the body in the bloodstream (8). Once the steroid hormone diffuses into a cell, it binds to certain receptors in the cytosol: glucocorticoid receptors (GR), as well as mineralocorticoid receptors (MR) (8). The MR is the receptor for the steroid hormone aldosterone which, as seen in Figure 5, has a very similar chemical structure as cortisol differing in only one carbonyl group (8). Consequently, MRs bind aldosterone but they also have a binding affinity for cortisol; while GRs can only bind cortisol (8).

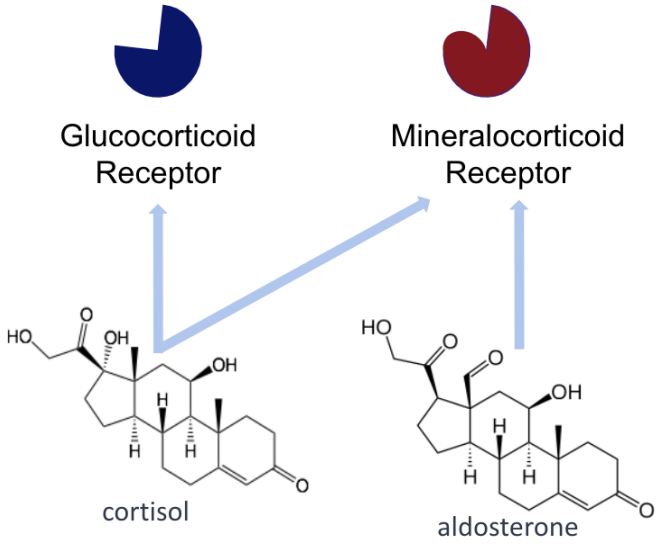

Figure 5. Diagram representing the cortisol binding affinities. The glucocorticoid receptor, represented in blue, has a strong binding affinity for cortisol. The mineralocorticoid receptor, represented in red, has binding affinity for both cortisol and aldosterone. Normally the aldosterone-MR complex facilitates regulation of blood pressure by mediating sodium and potassium levels (8).

As visible in Figure 6, the binding of cortisol to its intracellular receptor enables the modification of genes in the nucleus that facilitate many physiological activities including modulating the body's stress response (8).

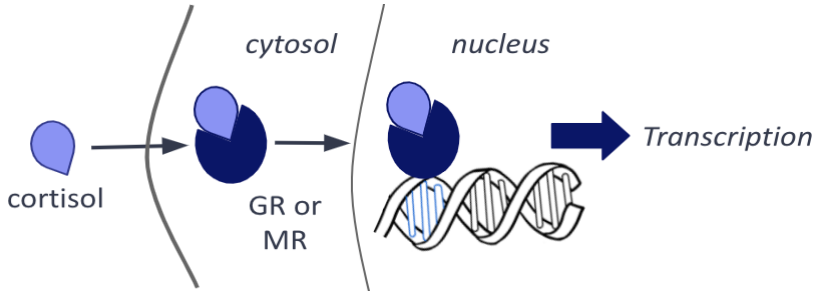

Figure 6. Diagram representing the cortisol reception and activity in the cell. Transcription of GR response elements contributes to the physiological events characteristic of the stress response.

Furthermore, the binding of cortisol to GRs mediates the negative feedback of the HPA axis, as seen in Figure 2. When cortisol levels have reached a certain threshold, the binding of the hormone to GRs inhibits the HPA axis at both the hypothalamus and the pituitary (8).

Consequently, if there is a genetic predisposition for hypersensitive GRs, this could contribute to diminished activity of the HPA axis and low basal cortisol levels.

While mineralocorticoid receptors do have regulatory effects on the HPA axis, MRs are restricted to limbic parts of the brain such as the hippocampus and the amygdala (20). Conversely, GRs are found throughout most regions of the brain, including the limbic system, and thus further mediates HPA axis inhibition (18). Consistent with what is observed in diseases relating to imbalances in cortisol levels, as described above, a review by Jacobson found that imbalances in HPA axis activity are associated with depression (9).

A genetic predisposition to an imbalance in cortisol-receptor sensitivity can be investigated through the analysis of particular genetic variations common among humans, known as single-nucleotide polymorphisms (SNPs) relating to reception of cortisol (16). A body of research has proposed certain genetic mutations, or SNPs, which account for an imbalance in cortisol receptor sensitivity and cortisol behavior has a role in a patient's vulnerability to depression (16; 17). These polymorphisms can be the difference of one nucleotide, as exemplified in Figure 7, which differentiates the wild type sequence from the mutant in the SNP rs41423247 known as the "bclI" SNP in the gene for GRs. Such a mutation modulates the sensitivity of the glucocorticoid receptor to cortisol (16).

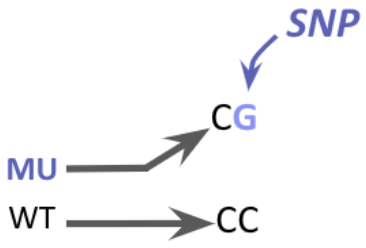

Figure 7. Depiction of the SNP rs41423247 (BCL1). WT represents the wild type sequence, while MUT depicts the mutant sequence for this SNP. (Adapted from 19).

In order to establish an understanding of genetic variations relating to extremes in cortisol sensitivity, the genotypes of particular SNPs corresponding to cortisol receptor sensitivity can be analyzed (16). SNPs that relate to GR or MR sensitivity can be characterized in order to better understand an individual's overall response to cortisol. For example, if an individual has a mutation which corresponds to low GR sensitivity to cortisol (GR resistance), their HPA axis will be less sensitive to regulating cortisol levels, hindering the negative feedback loop, and thus they will experience higher cortisol levels in the body. The opposite is true for GR hypersensitivity where the increased sensitivity to cortisol will reinforce the negative feedback loop of the HPA axis, consequentially diminishing cortisol levels in the body (20).

A study by Chen et al. has indicated that it is the interplay of genotypes that express hypersensitivity in one receptor and resistance in the other where normative brain function is negatively impacted (18). An individual with polymorphisms which account for GR resistance experiences GRs which are less stimulated by cortisol such that the negative feedback involved in the HPA axis is hindered contributing to heightened cortisol levels in the body (16). When paired with polymorphisms that facilitate hypersensitive MRs which are more sensitive to cortisol, the heightened levels of cortisol paired by the hypersensitive receptor may compound the effects of cortisol on the stress response facilitating adverse mental health symptoms such as depression.

Conversely, if polymorphisms account for GR hypersensitivity, the receptors are more stimulated by cortisol and thus will signal the negative feedback loop of the HPA axis and decrease cortisol levels (20). When paired with polymorphisms which contribute to MR resistance, where MRs are less sensitive to cortisol, this compounds to diminish the response to

cortisol because of both lower cortisol levels and decreased MR sensitivity, which may also be detrimental to mental health. These relationships are depicted in Figure 8.

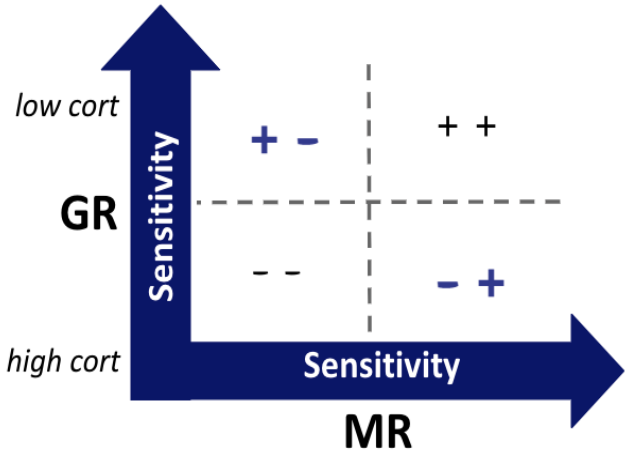

Figure 8. Diagram of the different genotypic combinations of receptor sensitivity with (+) indicating hypersensitivity and (-) indicating resistance. The first sign indicates the sensitivity of GR and the second represents sensitivity of MR. The combinations of high and low sensitivities of receptors are shown in green.

In order to develop an in-depth understanding of the interplay of cortisol receptor sensitivity, comprehension of the behavior of cortisol in the body must also be established. SNPs relating to cortisol transport, cortisol availability, and receptor inhibition and activity also need to be investigated. For example, the FKBP5 gene codes for a binding protein, or co-chaperone, that facilitates the binding of the glucocorticoid receptor so that the receptor can receive and bind cortisol to carry-out its functions throughout the body (16).

The diagnosis and treatment of depression can be an arduous process. According to the Diagnostic and Statistical Manual of Mental Health Disorders (DSM5), in order to be diagnosed, patients must experience two weeks of persistent symptoms such as depressed moods or loss of interest or pleasure (21). Additionally, patients can often go undiagnosed, and once diagnosed it can take a long time to find the right treatment (22). In this light, this study focused on investigating the genetic risk factors for depression in order to help make the diagnosis and treatment process for depression more efficient.

The current study proposes that genetic mutations which contribute to combinatorial effects of hypersensitive and resistant cortisol receptors facilitate an individual's heightened risk

for clinical depression. Analyzing genetic differences through SNPs relating to cortisol sensitivity in patients clinically diagnosed with depression may inform whether an imbalance in an individual's response to cortisol is linked to depression. If such a relationship can be established, this can provide physicians with a screening tool to better inform them of a patient's risk factors for depression.

Methods

This study consisted of 43 patients from Albany Medical College clinically diagnosed with depression. Each participant completed clinical assessments and DNA collection. Buccal swabs were administered, which sample DNA from the inside of the participant's cheek. DNA was extracted from each sample using a sodium hydroxide and Tris buffer method to extract the DNA from the buccal cells and isolate it using centrifugation as demonstrated in Figure 9.

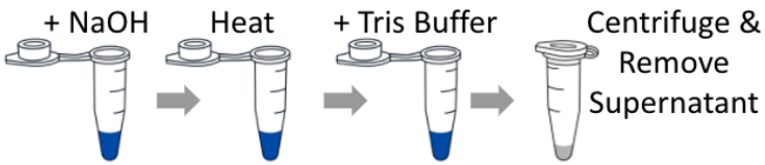

Figure 9. Depiction of the DNA extraction method where the DNA is removed from the supernatant and added to a new centrifuge tube to then be used for PCR templates.

A series of four different clinical assessments were administered for each patient. The Beck Depression Inventory (BDI) was administered in a series of self-report ratings (0-4 scale) to measure symptoms and behavior characteristic of depression (23). Data analysis focused particularly on questions 18 and 20: BDI question 18 refers to changes in sleeping patterns while BDI question 20 measures presence or loss of appetite. The State-Trait Anxiety Inventory (STAI) consists of a series of self-report ratings (0-4 scale) which are structured to measure either state—episodic—anxiety or trait—persistent—anxiety (24). The Adverse Childhood Events (ACE) assessment is a retroactive questionnaire which measures adverse childhood experiences with questions scored in categories of Abuse, Household Dysfunction, and Neglect in order to

determine a patient's increased risk for chronic stress (25). The Mindful Attention Awareness Scale (MAAS) consists of 15 self-report ratings (0-6 scale) which assess open awareness and attention to the present moment (26).

Quantitative Polymerase Chain Reaction (qPCR) was performed for each template with adequate amounts of DNA to allow for characterization of genotypes for various SNPs relating to both glucocorticoid and mineralocorticoid receptor activity, as well as the activity of cortisol. The specific SNPs that were analyzed, as well as the genes to which they belong, are depicted in Table 1.

Table 1. Depiction of the SNPs, the gene they belong to, and the function of those genes.

SNP	Gene	Role
RS11119328	11-beta hydroxysteroid dehydrogenase type I (11{beta}-HSD1)	Peripheral activation of cortisol from cortisone.
RS701950	11-beta hydroxysteroid dehydrogenase type I (11{beta}-HSD1)	Peripheral activation of cortisol from cortisone.
RS10515522	Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1)	Glucocorticoid receptor
RS33389	Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1)	Glucocorticoid receptor
RS5522	Nuclear Receptor Subfamily 3 Group C Member 2 (NR3C2)	Mineralocorticoid receptor
RS1360780	FK506 Binding Protein 5 (FKBP5)	Co-chaperone protein that modulates glucocorticoid receptor sensitivity.

In qPCR, a DNA template is mixed with DNA polymerase enzymes required for DNA elongation, RNA-DNA hybrid primers sets to target particular SNPs, free deoxynucleotides (dNTPs) as well as fluorescent probes which depict quantitative information about genotypes of SNPs in real time (27). Reagents from rhAMP SNP genotyping produced by Integrated DNA Technologies were used in this study. A qPCR machine modulates the temperature of the PCR reactions cycling ideal temperatures for denaturing double-stranded DNA, annealing primer sets, and extending the primer sets with dNTPs. This process is depicted in Figure 10. In order to differentiate genotypes, the two alleles are designated with different fluorescent dyes that are associated with each allele. In this way, differences in fluorescence produced during qPCR can be associated with the presence of a different allele and genotypes can be established (27).

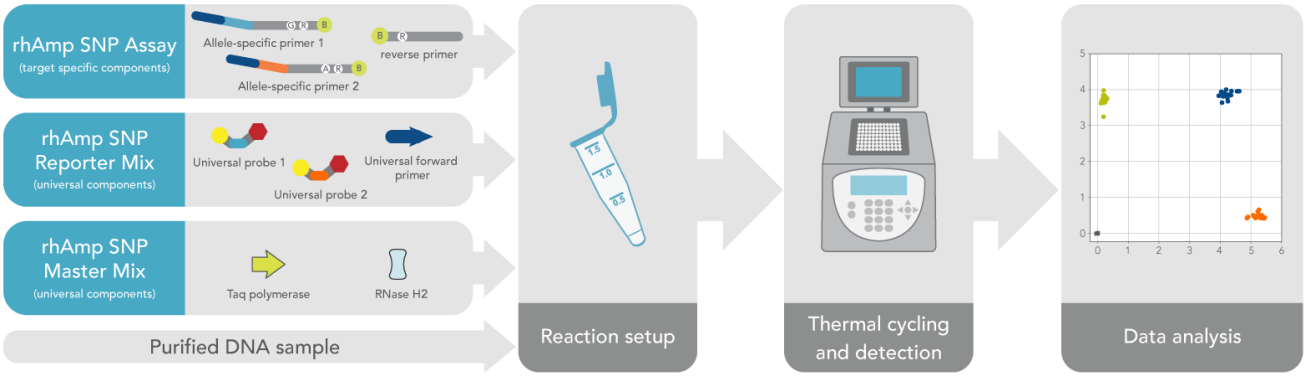

Figure 10. Depiction of Quantitative Polymerase Chain Reaction phases which differs from PCR due to the detection of fluorescence as a measure of DNA synthesis to indicate genotypes in real-time (27).

Data analysis was performed using JMP software. We used two-way ANOVAs and two-tailed T-tests to investigate correlations between SNP genotype and our clinical data.

Results

Results of statistical analysis of the measures of depression with regards to each SNP can be found in the Appendix. Although many of the comparisons did not show statistical significance, several were significant as described below.

Two SNPs were analyzed which were mutations of the 11-beta hydroxysteroid dehydrogenase type I (11β-HSD1) gene. This gene is responsible for the local, or peripheral, activation of cortisol from cortisone, as depicted in Figure 3. These SNPs were analyzed in order to gather a better understanding of the activation of cortisol throughout the body. Studies have shown that known polymorphisms increase peripheral cortisol activation, and therefore increase the conversion of cortisone to cortisol (28). ANOVAs and T-tests performed for clinical data and RS1119328, which is associated with increasing cortisol activation, revealed several significant findings. Patients who are heterozygous for the RS11119328 SNP reported significantly lower scores in the STAI, indicating lower trait anxiety, compared to patients who were homozygous wild type for this SNP, as seen in Figure 11a. Patients who are heterozygous for the RS11119328 SNP also reported significantly lower ACE-Abuse scores, as well as significantly lower total sum scores for the ACE scale, compared to patients who are homozygous wild type for this SNP, as seen in Figure 11b and 11c respectively. It is however important to note that there were no patients who were homozygous mutants for this SNP.

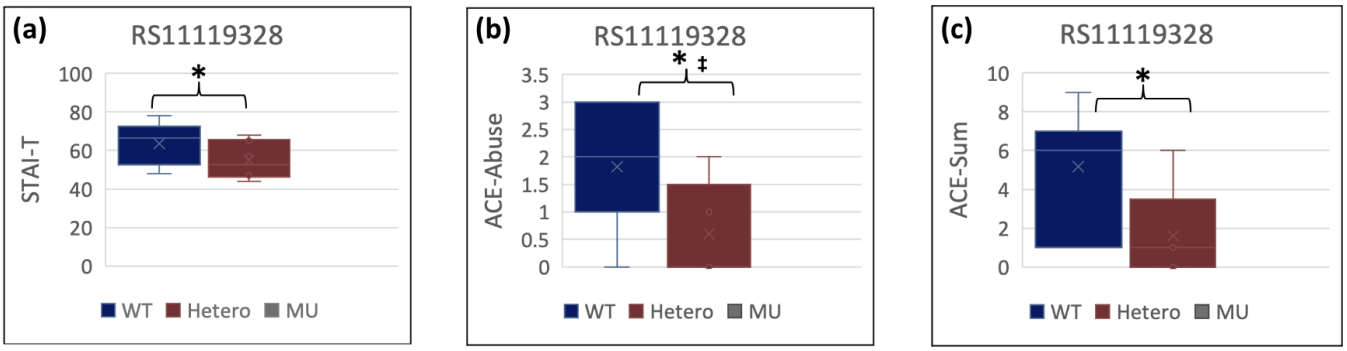

Figure 11. Box-and-Whisker Plots which depict the significant findings for ANOVAs and T-tests for RS1119328 and the clinical data. The * symbol indicates significant ANOVA results while the ‡ symbol indicates significant T-test findings. Plot (a) depicts the genotypes for RS11119328 by the STAI-T scores. Significant differences are found between homozygous wild types, represented by blue, and heterozygotes, represented by red. Plot (b) depicts the genotypes for RS11119328 by the ACE-Abuse scores. Significant differences are found between homozygous wild types, represented by blue and heterozygotes, represented by red. Plot (c) depicts the genotypes for RS11119328 by the sum of ACE scale scores. Significant differences are found between homozygous wild types, represented by blue, and heterozygotes, represented by red.

ANOVAs and T-tests performed for clinical data and RS701950, which is also associated with increased peripheral cortisol activation, revealed certain patterns across genotypes. Patients homozygous wild-type for RS701950 scored slightly lower in STAI-Sum than both patients who were heterozygotes and homozygous mutants (p=0.0738), as seen in Figure 12. However, the homozygous wild type sample size is very small and thus this is not a significant finding.

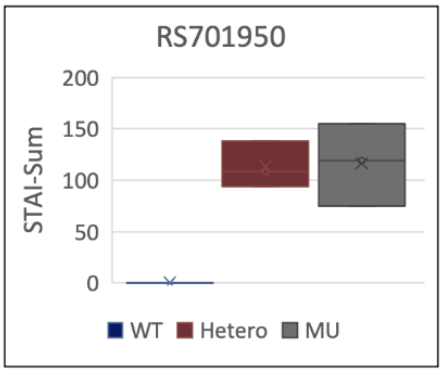

Figure 12. Box-and-Whisker Plots which depict the findings for ANOVAs and T-tests for SNP RS701950 and sum scores for STAI.

Two different polymorphisms of the Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1), also known as the glucocorticoid receptor, were analyzed against clinical data and revealed significant findings. Known polymorphisms for NR3C1 have been identified to either increase or decrease glucocorticoid receptor sensitivity based on the particular SNP (13). This study investigated SNP RS33389 and RS10515522 which have been found to increase glucocorticoid receptor sensitivity (29). ANOVAs and T-tests indicated that patients who were homozygous for the mutant allele of RS33389 scored significantly higher on BDI question 18 than patients who were homozygous wild type for RS33389, as seen in Figure 13. Question 18 of the Beck Depression Inventory gauges the patients average duration or amount of sleep. Significantly higher question 18 scores indicating patients with two mutant alleles for RS33389 report significantly increased sleep compared to those with two wild type alleles.

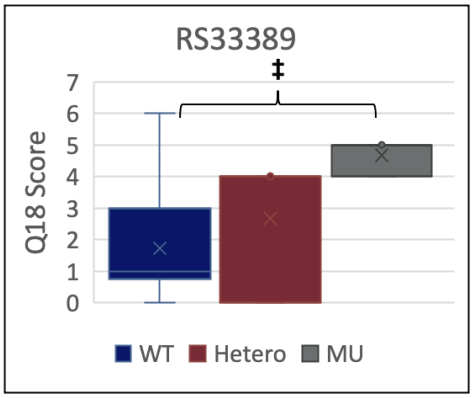

Figure 13. Box-and-Whisker Plots which depict the significant findings for ANOVAs for SNP RS33389 and Question 18 scores. Significant differences are found between homozygous wild types, represented by blue, and homozygous mutants, represented by gray.

ANOVAS and T-tests for RS10515522 and clinical data revealed no significant findings. Nevertheless, there were trends which are consistent with expected results. ANOVAs and T-tests for RS10515522 and Neglect scores for ACE scales revealed that patients who were homozygous mutant for this SNP scored higher in Neglect than patients who were homozygous wild type and those who were heterozygous for RS10515522, as seen in Figure 14. However, it

is important to note that the sample size for RS10515522 homozygous mutants was 2 and therefore these findings are not statistically significant.

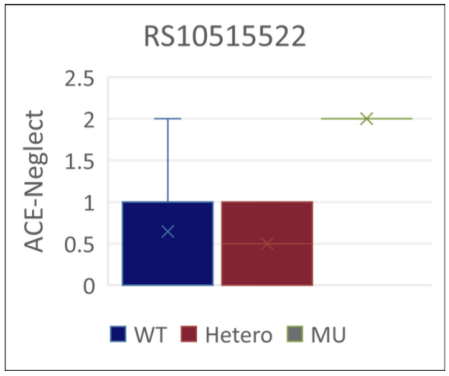

Figure 14. Box-and-Whisker Plots which depict the significant findings for ANOVAs for SNP RS10515522 and ACE Neglect scores.

A polymorphism of the Nuclear Receptor Subfamily 3 Group C Member 2 (NR3C2) was also analyzed against clinical data and revealed significant findings. The NR3C2 gene encodes the mineralocorticoid receptor. Known polymorphisms for NR3C2 have been identified to decrease mineralocorticoid receptor sensitivity, or make it less responsive to cortisol and aldosterone (30). Such polymorphisms have been studied to contribute, at least in part, to both psychiatric and cardiovascular symptoms; illustrating the consequentially altered effects of not only cortisol, but also aldosterone (30, 31). This study investigated the patterns in genotypes of the SNP RS5522 by the clinical assessments that were administered. ANOVAs and T-tests indicated that patients who are heterozygous for the RS5522 SNP, score significantly lower on the MAAS compared to homozygous wild type patients, as seen in Figure 15. This indicates that patients with at least one mutant RS5522 allele report overall lower levels of mindfulness and attention. However, it is also important to note that there are no patients who were homozygous mutant who could be analyzed for SNP RS5522 and MAAS scores.

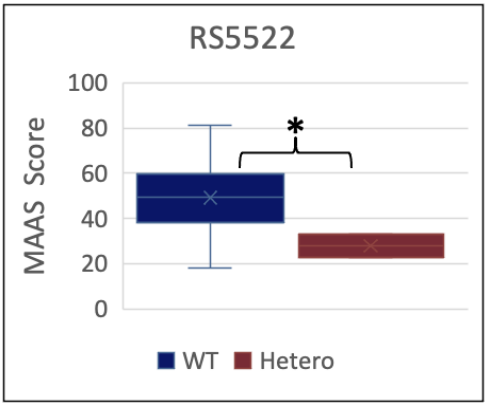

Figure 15. Box-and-Whisker Plots which depict the significant findings for ANOVAs for SNP RS552 and MAAS scores. Significant differences are found between homozygous wild types, represented by blue, and heterozygotes, represented by red.

A polymorphism of the FK506 Binding Protein 5 gene was also analyzed against clinical data. FK506 Binding Protein 5 (FKBP5) is a co-chaperone protein that decreases glucocorticoid receptor sensitivity by binding to the cortisol-receptor complex, after cortisol has bound to its receptor, and causes a decrease in the GR binding affinity. This makes cortisol binding less favorable and thus FKBP5 acts as a localized feedback loop for GR sensitivity (32). Known polymorphisms increase the activity of this co-chaperone FKBP5 therefore contributing to decreased GR sensitivity (32). This study analyzed the SNP RS1360780; ANOVAs and T-tests revealed that patients who were homozygous wild-types scored lower on BDI question 18 compared to patients who were heterozygotes for RS1360780, as seen in Figure 16. While these findings were not significant, they support the significant findings for RS33389 which indicate patients who have at least one mutant allele report a greater duration of sleep.

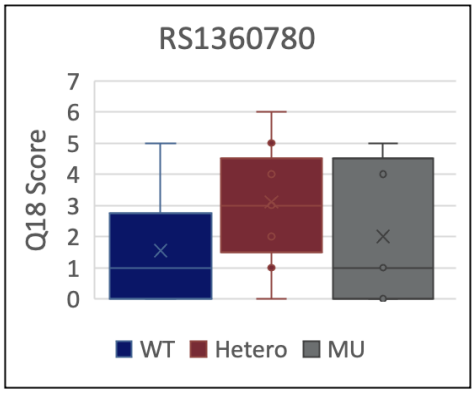

Figure 16. Box-and-Whisker Plots which depict the significant findings for ANOVAs for SNP RS1360780 and BDI question 18 scores.

Discussion

Some patterns of significance were identified across the various SNPs that were analyzed in this study. Patients who were heterozygous for the SNP RS1119328, a polymorphism of the 11β-HSD1 gene, reported significantly lower trait anxiety scores in the STAI-T, significantly lower ACE-Abuse scores, and significantly lower sum ACE scores. These findings are consistent with cortisol's role in coping with stressful situations (33). Cortisol is secreted in response to stimuli which allow for the body to be prepped for the sympathetic stress response during the fight or flight reaction (5). It follows that increased stressful stimuli or chronic stress would cause increased preparation or coping ability for stressful situations (33). Therefore, patients with at least one mutant RS1119328 allele may have increased cortisol sensitivity which allows them to be more prepared to cope with stress. As a result, it is possible these patients perceive stressful situations to be less stressful and thus they report less trait anxiety and less adverse childhood experiences.

Patients who were homozygous mutant for the SNP RS33389, a polymorphism of the NR3C1 gene which encodes GRs, scored significantly on BDI question 18, indicating significantly increased duration of sleep, compared to patients who were homozygous wild type

for this SNP. This is consistent with excessive sleep as a symptom of clinical depression. This could potentially be explained by cortisol's effects on sleep. As part of the stress response, cortisol stimulates arousal or wakefulness and inhibits rapid-eye-movement (REM) sleep (5). Studies have found REM sleep to be important for memory formation, learning, neurodevelopment and neuroplasticity (34). Oftentimes in studies where REM sleep is deprived, subjects have a greater rebound sleep, or experience increased pressure or need to sleep (34). Therefore, the increased wakefulness and decrease in this phase of sleep could facilitate the need for more sleep, leading to the excessive sleep symptom seen in patients with clinical depression.

Patients who were heterozygous for the SNP RS5522, a polymorphism of the NR3C2 gene which encodes MRs, scored significantly lower on the Mindful Attention Awareness Scale than patients who were homozygous wild type. This is consistent with cortisol's role in increasing attention and arousal (35). In increasing arousal and attention, cortisol facilitates preparation for the fight or flight response. However, the pattern observed in this study could be explained by this polymorphism facilitating MR resistance and thus decreased cortisol effects, accounting for the decreased attention.

While some patterns of significance were observed, there were not sufficient findings to support our hypothesis that combinatorial effects of cortisol hypersensitivity and resistance increase risk for depression. With future research, increasing sample size will allow for a more well-rounded understanding of the relationship between cortisol receptor sensitivity and depression. Furthermore, genotyping the samples with additional SNPs will provide more insight into cortisol sensitivity and regulation.

If such a relationship in cortisol sensitivity can be established as a predictor for depression, this could provide physicians with a genetic screening tool to help identify patients at

increased risk for depression. By alleviating the many pitfalls of prolonged diagnosis and treatment, genetic testing may be done to indicate predictors for depression before the patient has endured weeks or more of depressive symptomology.

Additionally, once this relationship is established, it could help create a personalized treatment method for depression related to imbalances in cortisol sensitivity. While certain drugs exist which alter neurotransmitter effects, these treatment methods may not be treating the entire chemical causes for depression, and often add-on treatments are employed in combination with already-existing neurotransmitter modulators (36). To treat the endocrine components of depression, there is a medication that may be applied to treat imbalances in cortisol sensitivity relating to depression. The drug RU486, commonly known as mifepristone, was originally produced to be used for chemical abortions (37). This is because RU486 is an antagonist to the progesterone receptor (37). Progesterone helps maintain the endometrial lining and prevent menstruation which helps the maturation of the zygote. Mifepristone blocks the progesterone receptor such that the effects of progesterone are inhibited and there is a shedding of the endometrial lining, ceasing a potential pregnancy. RU486 is also an antagonist to the glucocorticoid receptor (37). Mifepristone has been used to treat post-traumatic stress disorder (PTSD) and schizophrenia (38, 39). As the drug can diminish the effects of cortisol by blocking the GR, RU486 may also be a treatment method for certain types of depression relating to imbalances in cortisol receptor sensitivity. Therefore, once the genetic markers relating to combinatorial imbalances in cortisol receptor sensitivity have been supported to be risk factors for depression, diagnosis and treatment of clinical depression can be made more efficient for the physician and the patient.

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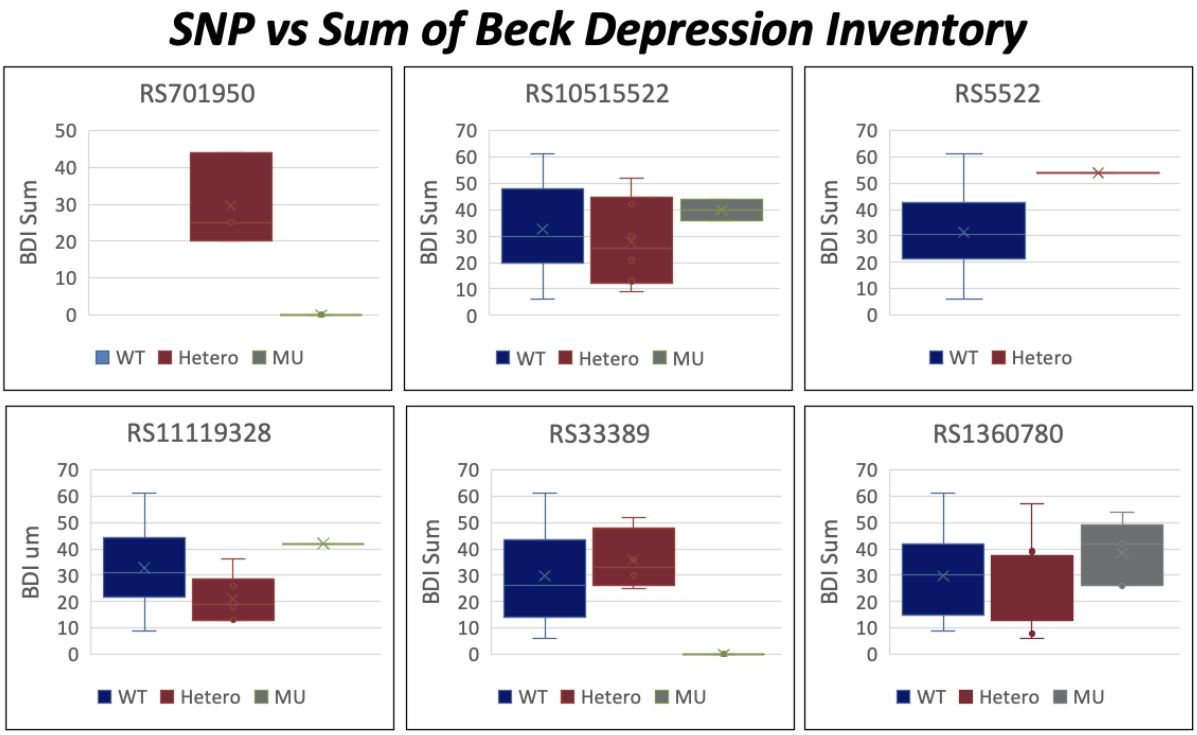
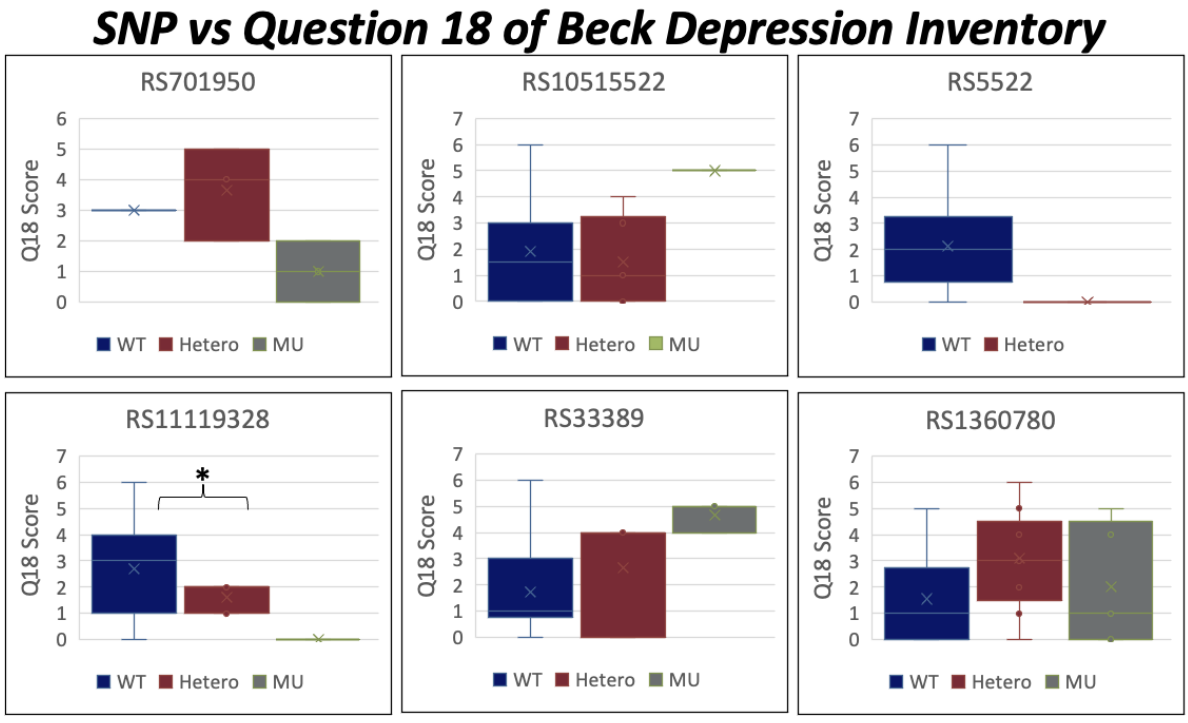
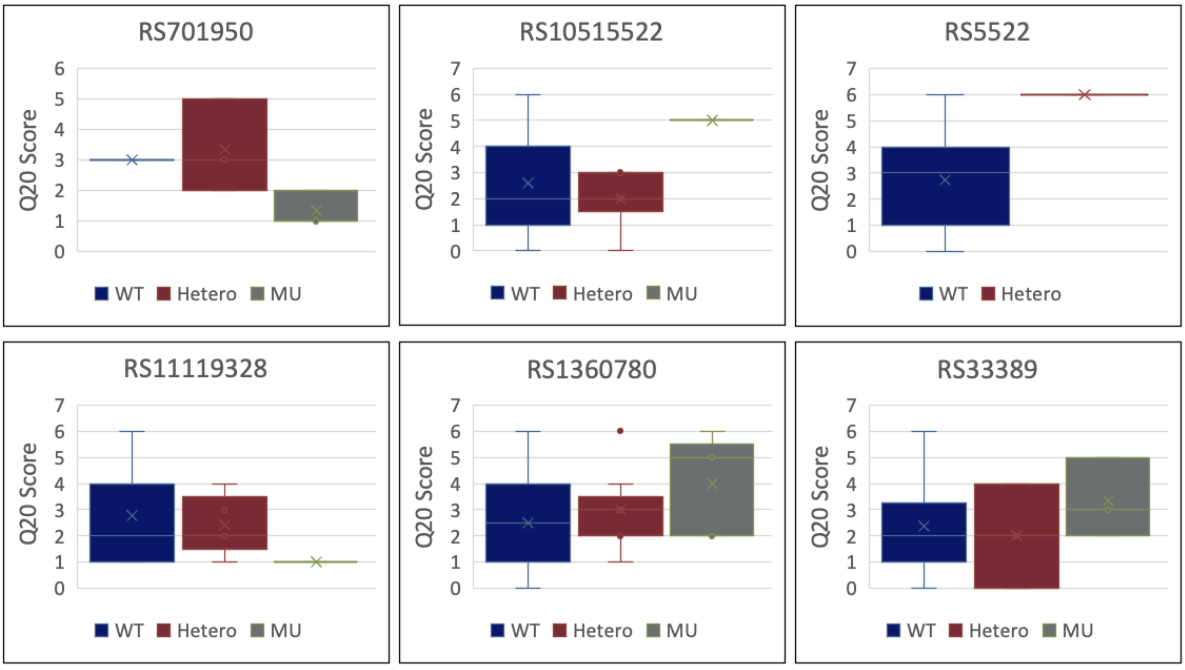
Appendix

Box-and-whisker plots of all clinical data and SNPs, grouped by clinical assessments.

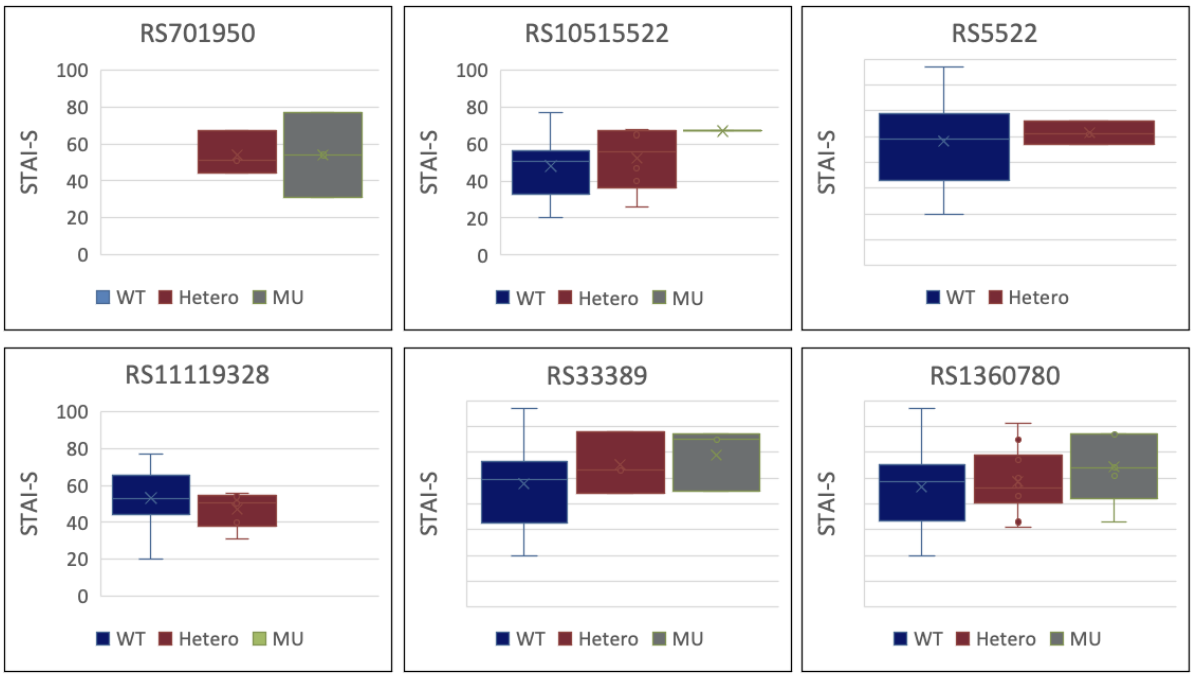




SNP vs Question 20 of Beck Depression Inventory



SNP vs State Scale of State-Trait Anxiety Index



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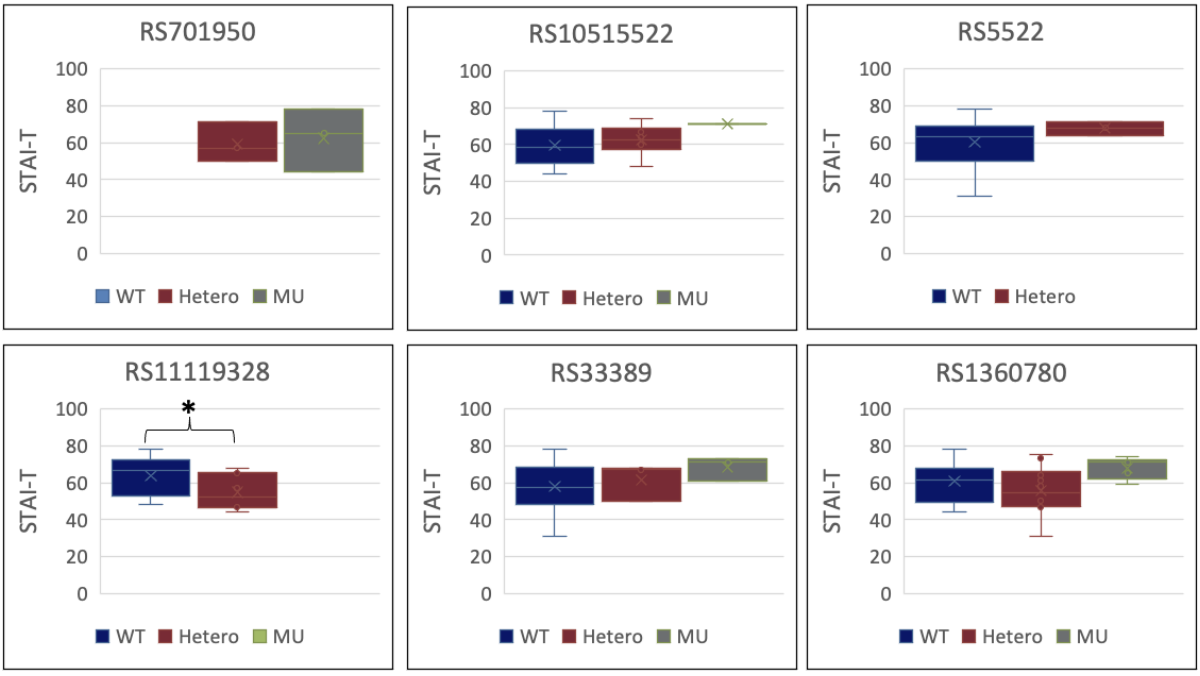
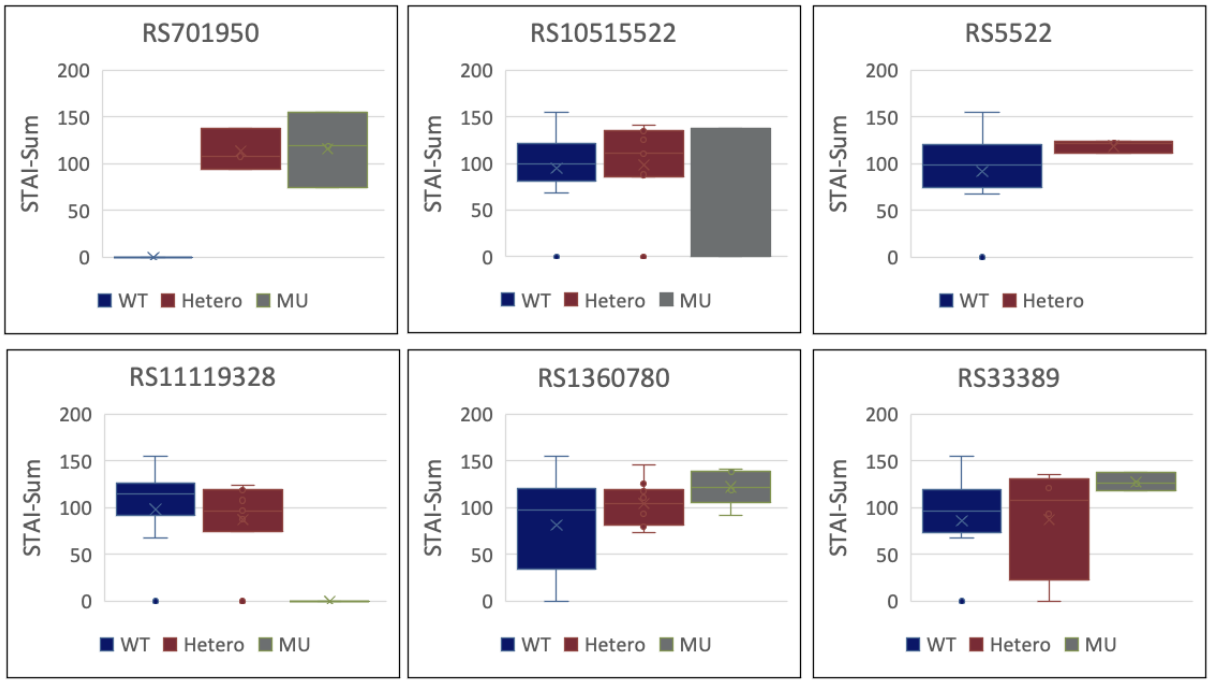
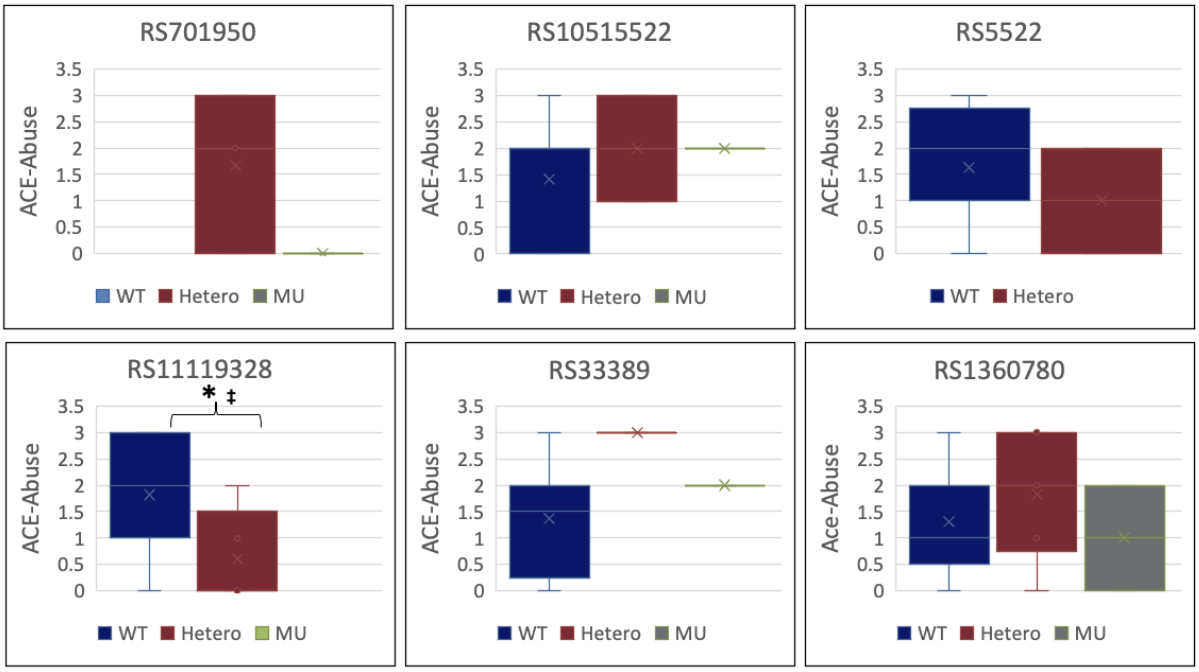


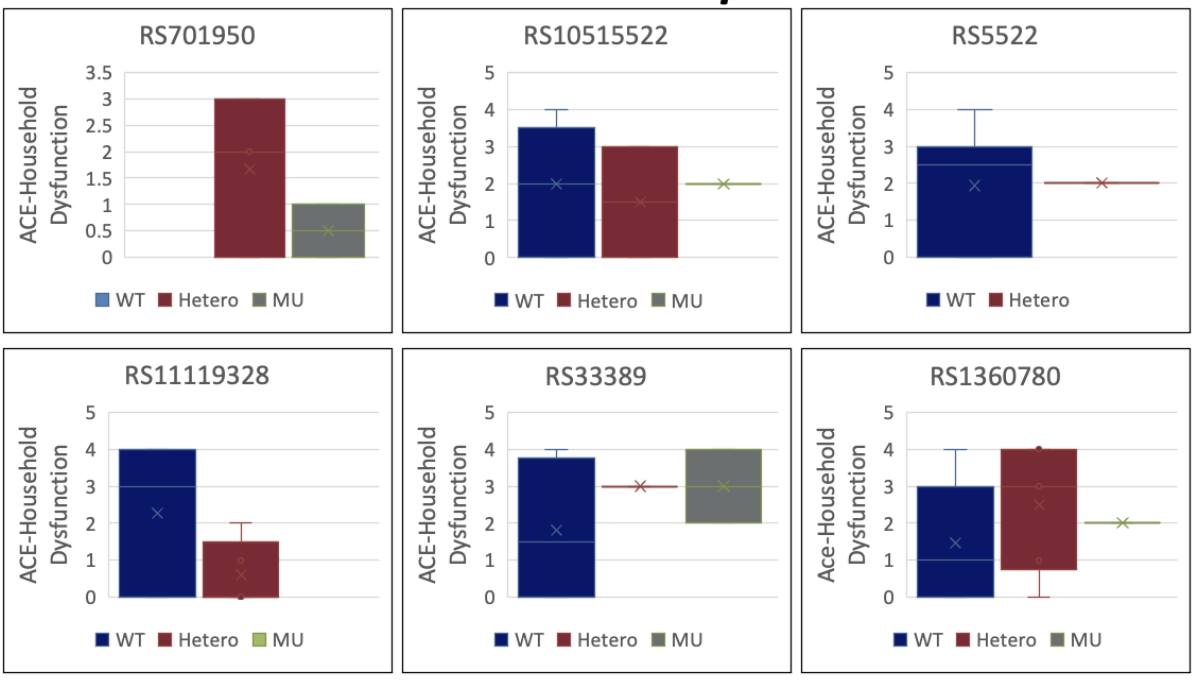
SNP vs Sum of State-Trait Anxiety Index



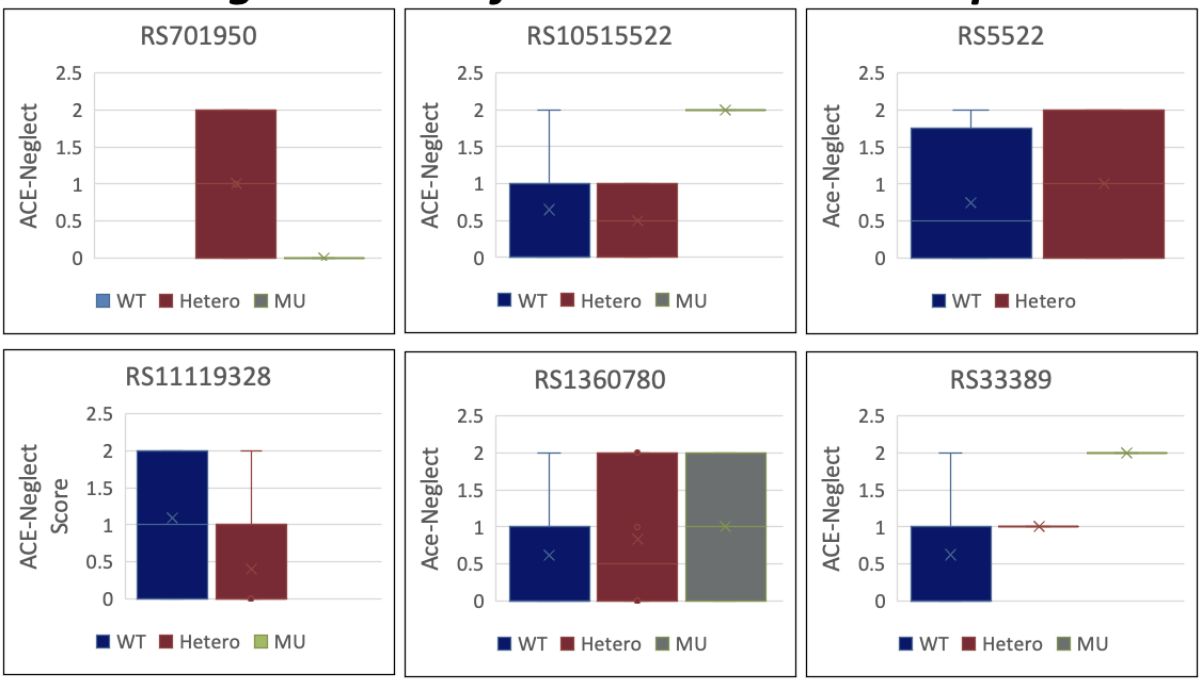
SNP vs Abuse Score of Adverse Childhood Experiences



SNP vs Household Dysfunction Score of Adverse Childhood Experiences



SNP vs Neglect Score of Adverse Childhood Experiences



SNP vs Sum of Adverse Childhood Experiences