ABSTRACT
Background: Bipolar disorder (BD) is characterized by episodes of mania and depression. The specific number of susceptibility loci, the recurrence risk ratio attributable to each locus, and the degree of interaction between loci are unknown. By determining which single nucleotide polymorphisms (SNPs) or copy number variants (CNVs) predispose individuals to BD, possible mechanisms of disease may be elucidated.
Method: A Genome Wide Association Study (GWAS) was performed using cases of BD and normal controls. SNPs between cases and controls were compared using a modified t-test. A sliding window analysis was performed on SNPs stratified by chromosome and locus. The mean probe intensities of cases and controls from statistically significant regions were then reanalyzed for differences.
Results: Findings suggest many SNPs and CNVs may have involvement in the pathophysiology of BD. Of greatest significance were the SNPs within the HTR4 and CAMTA1 genes and 3 genomic regions residing within the Neuron Navigator 2 (NAV2) gene, the Down Syndrome Cell Adhesion Molecule Like 1 (DSCAML1) gene, and the Voltage-dependent Calcium Channel Alpha 1G (CACNA1G) gene.
Conclusion: Multiple SNPs and CNVs may play a role in the phenotype of Bipolar Disorder. A convergent functional genomics approach with a role in the phenotype of Bipolar Disorder. A convergent functional genomics approach with a role in the phenotype of Bipolar Disorder. A convergent functional genomics approach with a role in the phenotype of Bipolar Disorder.

INTRODUCTION
Bipolar Disorder has a clear and recognized genetic component with 50 percent of patients having a family history of the disorder. This is further evidenced by a 40-50 percent concordance rate for monzygotic twins and a 10-20% concordance rate in dizygotic twins. Importantly, the mode of inheritance of BD is complex and likely multifactorial. Genome Wide Association Studies (GWAS) are case-control studies that compare hundreds of thousands of single nucleotide polymorphisms between individuals with disease and individuals without disease. Analysis of copy number variants (CNVs) have come to the forefront of genetic research recently with the link to disease risk being demonstrated in various psychiatric diseases.

METHODS
A European cohort of 2205 individuals was genotyped using Affymetrix® Genome-Wide Human SNP Array 6.0. Mean probe intensities for each of the arrays were calculated and 959 individuals were removed due to low intensity thresholds. The probe intensities of each SNP of the remaining 1610 cases and controls were normalized to the mean intensity of the SNP probes across all the arrays. The log2(a+b), was calculated for each SNP, where “a” and “b” represent the intensity of the SNP. The data was normalized using the quantile range of the dataset. A modified students t-test algorithm was used to generate t-values for each of the 906600 SNPs of the cases and controls. P-values for each of these probes were subsequently generated. The theory is that if there is a contiguous series of SNPs with low p-values then this may represent a CNV. 4 regions of interest were identified and the normalized log2(a+b) values for 745 SNPs, were extracted into separate files for further analysis. The mean intensities of the cases and controls were run against a simple students t-test and p-values were generated.

RESULTS
Table 1: Top 9 SNPs

Table 1 shows the top 9 SNPs that achieved p-values that approached genome wide significance. The SNP (rs12275038) with the lowest p-value was the located within the Neuron Navigator 2 (NAV2) gene, the Down Syndrome Cell Adhesion Molecule Like 1 (DSCAML1) gene, and the Voltage-dependent Calcium Channel Alpha 1G (CACNA1G) gene. The NAV2 gene has been associated with autosomal dominant non-syndromic hearing impairment. NAV2 is also implicated in non-syndromic Bardet-Biedl syndrome. The DSCAML1 gene is involved in the neural development and is detected in multiple regions of the brain involved in cognition. The CACNA1G gene has been associated with a psychiatric illness, codes for a voltage-sensitive calcium channel, which may participate in neurotransmitter release in multiple types of neurons. The DSCAML1 is involved in the neural development and is detected in multiple regions of the brain involved in cognition. The CACNA1G gene has been associated with a psychiatric illness, codes for a voltage-sensitive calcium channel, which may participate in neurotransmitter release in multiple types of neurons.

DISCUSSION
Analysis of SNPs and CNVs yielded several interesting genes implicated in cognitive function and psychiatric disease. HTR4 is part of the family of serotonin receptors, which influences dopamine secretion, and has been implicated in both bipolar disorder and schizophrenia. CAMTA1 has been implicated in cognitive decline in the elderly. It is known that NAV2 plays a significant role in embryonic neuronal development. A dysfunction in NAV2 may be a causative factor since bipolar patients showed neuronal and glial atrophy. The CACNA1G gene has been associated with a psychiatric illness, codes for a voltage-sensitive calcium channel, which may participate in neurotransmitter release in multiple types of neurons. The DSCAML1 is involved in the neural development and is detected in multiple regions of the brain involved in cognition. Additionally, this study provides new evidence that copy number variants may play a role in the pathophysiology of bipolar disorder and provides loci of interest for further research and study. This study also shows that there may be some utility in looking at the raw probe intensities post GWAS analysis for verification CNVs.

CONCLUSION
This study found additional evidence for multiple polymorphisms involved in BD as well as common polymorphisms found in BD, ADHD and schizophrenia. Additionally, this study provides new evidence that copy number variants may play a role in the pathophysiology of bipolar disorder and provides loci of interest for further research and study. This study also shows that there may be some utility in looking at the raw probe intensities post GWAS analysis for verification CNVs.

ACKNOWLEDGEMENTS
Thanks is given to my mentor Dr. David Craig for his guidance, support, advice and encouragement. I would also like to thank Alexis (Tarzan) Christoforides for the analysis of these data sets possible.

REFERENCES