TABLE OF CONTENTS

ABSTRACT	i-iii
DISSEMINATIONS OF THESIS CONTENT	iv
DECLARATION	v
CERTIFICATE OF SUPERVISOR	vi
ACKNOWLEDGEMENT	vii-viii
LIST OF FIGURES	xiv-xvii
LIST OF TABLES	xviii-xix
LIST OF ABBREVIATIONS	xx-xxiv

CHAPTER I: INTRODUCTION 1-10

CHAPTER II: REVIEW OF LITERATURE 11-23

2.1.1.	Hallmarks of cancer	12-13
2.1.2.	Genomic instability	14-15
2.1.3.	Evading immune destruction	15-16
2.2.1.	Genomic instability in immune related genes	16
2.2.2.	Avoiding immune recognition	16
2.2.3.	Inducing immune suppressive microenvironment	17
2.3.1.	Mutations in immune related genes	17
2.3.2.	CNA in immune related genes	17
2.4.1.	Frequently mutated genes in cancer	17-18
2.4.2.	PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha)	18-19
2.4.3.	TG (Thyroglobulin)	19

2.4.4.	HLA-A and HLA-B	19-20
2.4.5.	HLA-DRB1	20
2.4.6.	CIITA	20
2.5.1.	G-quadruplex	21-22
2.5.2.	G-quadruplex in immune system	22
2.5.3.	G-quadruplex in cancer- can generate genomic instability	23

CHAPTER III: MATERIALS AND METHODS 25-33

3.1.1.	Data collection	26-29
3.1.2.	Analysis of alterations in the DNA sequence of the immune related genes	29-30
3.1.3.	Survival analysis considering mutations	30
3.1.4.	Identification of differentially expressed genes (DEGs)	30
3.1.5.	Identification of over-represented pathways	30
3.1.6.	Estimating infiltration of immune cell to the tumor immune microenvironment	30-31
3.1.7.	Statistical analysis and data visualization	31
3.2.1.	Expression of 4genes (HLA-A, HLA-B, HLA-DRB1 and CIITA) and survival analysis	31
3.2.2.	Relationship Between 4genes (HLA-A, HLA-B, HLA-DRB1 and CIITA) and immune infiltration in the tumor microenvironment	31
3.2.3.	Correlation between 4genes (HLA-A, HLA-B, HLA-DRB1 and CIITA) and HLA-E	32

3.3.1.	Identification of putative G-quadruplex in human genome	32
3.3.2.	Visualization of overlap between G4 structures and immune-related genes	32
3.3.3.	Annotation of putative G4 locations onto human genome	32
3.3.4.	Analyzing the density of G4	33
3.3.5.	Examining the frequency of mutations in G4 locations	33

CHAPTER IV: RESULTS AND DISCUSSION

4.1	Characterization of immune related genes with genomic instability in the human genome with respect to cancer	35-68
4.1.1.	Results	35-64
4.1.1.1.	Mutational summary of immune related genes in 24 cancer types	35-45
4.1.1.2.	Frequency of mutated genes in 24 different cancer types	46-51
4.1.1.3.	CNA in frequently mutated immune genes	52-59
4.1.1.4.	G-quadruplexes (G4) and the genes related to immune system mapped onto human genome	59
4.1.1.5.	G4 density in genes and promoters of immune genes, housekeeping genes and proto-oncogenes	60-61
4.1.1.6.	G4 density in genes and promoters of immune classes and proto-oncogenes	61-63
4.1.1.7.	Mutations in G4 of the immune system	64

4.1.2.	Discussion	65-68
4.2.	Functional analysis of immune related genes with genomic instability	69-103
4.2.1.	Results:	69-100
4.2.1.1.	Kaplan Meier survival curves for PIK3CA mutations	69-71
4.2.1.2.	Cox- regression analysis of both mutated and non-mutated PIK3CA dataset	72
4.2.1.3.	Kaplan Meier survival curves for TG mutations	73-74
4.2.1.4.	Survival data for mutations of the 4 antigen presentation genes	74-82
4.2.1.5.	Survival analysis considering expression levels of the 4 antigen presenting genes	83-100
4.2.2.	Discussion	101-103
4.3.	Investigating the crucial role of immune related genes with genomic instability in different type of cancer	104-127
4.3.1.	Results	104-123
4.3.1.1.	Over-represented pathways in PIK3CA mutated datasets	104
4.3.1.2.	Differentially expressed genes in complement and coagulation pathway	105-108
4.3.1.3.	Difference in immune infiltration to tumor microenvironment in mutated versus non-mutated PIK3CA samples and their association to differentially expressed genes	109-111
4.3.1.4.	Over-represented pathways in TG mutated datasets	112

4.3.1.5.	Difference in immune infiltration to tumor microenvironment in mutated and non-mutated TG samples of BRCA	113-114
4.3.1.6.	Differential expression of CIITA, RFX (RFXANK, RFXAP, RFX5), CREB, NFY (NFYA, NFYB, NFYC), HLA-A, HLA-B, HLADRB1, HLA-E and HLA-G in LGG	115-117
4.3.1.7.	Influence of RFX (RFXANK, RFXAP, RFX5), CREB, NFY (NFYA, NFYB, and NFYC), HLA-E and HLA-G expression on survival in LGG	118-120
4.3.1.8.	Correlation between 4genes in our study (HLA-A, HLA-B, HLA-DRB1 and CIITA) and infiltrating immune cells	121-122
4.3.1.9.	Correlation between 4genes (HLA-A, HLA-B, HLA-DRB1 and CIITA) and HLA-E	122
4.3.1.10.	Correlation among CIITA, RFXANK, RFXAP, RFX5, CREB, HLA-A, HLA-B, HLA-DRB1 and HLA-E.	122-123
4.3.2.	Discussion	124-127

CHAPTER V: SUMMARY AND CONCLUSION 128-131

CHAPTER VI: REFERENCES 132-135

SUPPLEMENTARY 136-155