INTERLEUKIN-6, ITS SUBUNIT gp 130 AND THE POTENTIAL RISK OF PROSTATE CANCER IN A POPULATION OF MEN FROM TOBAGO

by

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INTERLEUKIN-6 ITS SUBUNIT gp130 AND THE POTENTIAL RISK OF PROSTATE CANCER IN A POPULATION OF MEN FROM TOBAGO

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Prostate cancer is a public health concern, particularly to the African-American community. African-American men are disproportionately affected and experience prostate cancer rates about 60% more often than white Americans. It is the second leading cancer in men and it is second only to lung cancer in cancer related deaths. This is a significant public health problem. This paper will focus on the gene Interleukin 6 signal transducer isoform 1 (IL6ST), on chromosome 5q11.2, with polymorphisms relating to gp130 [rs 3730293 and rs 3729960]; both single nucleotide polymorphisms result in an amino acid change. The change is Glycine to Arginine for rs 3729960 which is located in exon 14 and Isoleucine to Threonine for rs 3730293 which is located in exon 10. Human IL-6 signaling requires the 80kDa IL-6R receptor, which is responsible for IL-6 specificity and the 130kDa glycoprotein, gp130, the signal transduction subunit for signal transduction to occur. IL-6 acts through its receptors which are polymorphic, and subsequently may cause it to have different functionality. A population based case/control study was conducted to evaluate the influence of gp130 snps on prostate cancer risk in an Afro-Caribbean male population of Tobago. This population was chosen because of the high prevalence of prostate cancer. A subset of 1000 samples taken from a study done by Bunker et al, was genotyped by PCR and fluorescence polarization methods. Statistical analysis yielded all

estimated allele frequencies to be in Hardy Weinberg Equilibrium. Chi square analysis of the cases and controls yielded no significant association of the gp130 snps and prostate cancer risk.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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1.0 INTRODUCTION

Prostate cancer is a disease where by cancer develops in the prostate, a gland in the human male reproductive system. The prostate is a male reproductive organ that both creates and stores seminal fluid. The prostate is a walnut sized gland located in front of the rectum and underneath the urinary bladder of men.

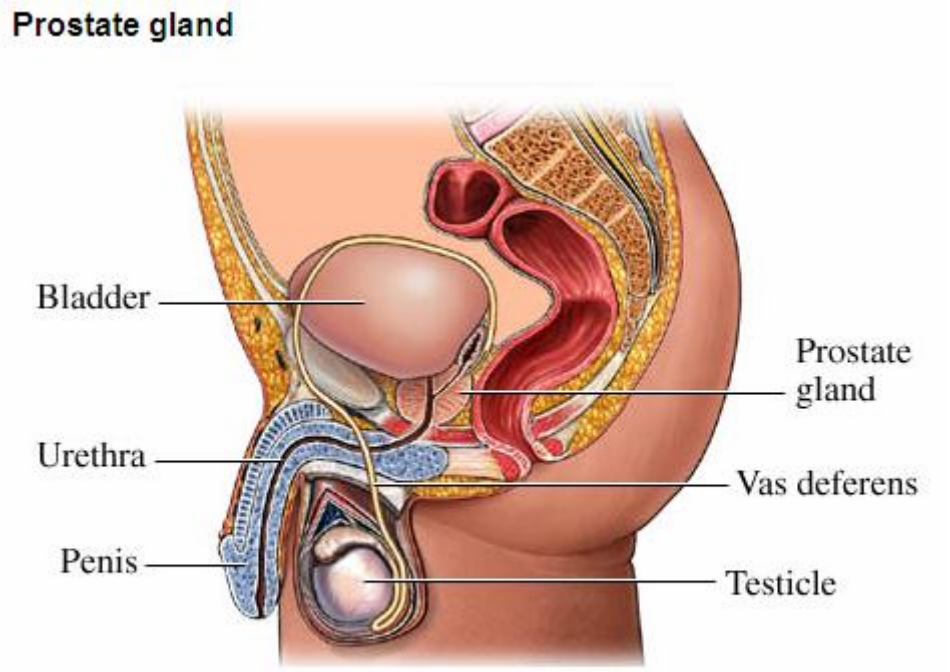


Figure 1: Diagram showing the position of the prostate gland

Figure 1 taken from www.liv.ac.uk/researchintelligence/issue21/prostatecancer.html

Clinically evident prostate cancer can be established by tissue diagnosis following clinical suspicion based on an abnormal TRUS (transrectal ultrasound), an elevation in serum PSA (prostate specific antigen) levels, an abnormal DRE (digital rectal exam) and a histological examination of a prostate tumor from a biopsy. (http://www.cancer.org) Prostate cancer typically develops in men over age 50. It is the second leading cancer in men and it is second only to lung cancer in cancer-related deaths (http://cancer.gov). The American Cancer society suggests that annual medical examinations for men include a DRE and a PSA determination. These examinations should begin at age 50 for men with life expectancies of at least 10 years or age 45 for African-American men and men with a family history of the disease (Bunker et al, 2004). In 2005, according to the National Cancer Society, prostate cancer was responsible for 232,090 new cases with an estimated 30,350 deaths (http://www.seer.cancer.gov). African-Americans are disproportionately affected, experiencing prostate cancer about 60% more often than white Americans. African-American men also present with the highest chance of being diagnosed at an advanced stage of prostate cancer and they are more likely to die from prostate cancer than any other race/ethnicity of people residing the United States (Freedland et al, 2004). Both the Afro-Caribbean population and African-American population have West African ancestry due to the enslavement process that took place throughout the 18th and 19th centuries on both the island of Tobago and in the United States. In fact, African ancestry has been linked to prostate cancer among males living throughout the Western Hemisphere (Shea et al, 2002).

In addition to ethnicity, a positive family history can be a significant risk factor for the development of prostate cancer (Nieder et al, 2003). Some families may present a Mendelian

pattern of inheritance, Carter et al provided evidence for a familial clustering of prostate cancer that they attributed to an autosomal dominant mode of inheritance (Carter et al, 1992), still other families will present with an inheritance pattern termed "Familial Prostate Cancer", whereby having as few as one affected relative will contribute to prostate cancer risk (Steinberg et al, 1990). Heritable genetic effects have been found in twin studies which were conducted in Finland that also support the idea of prostate cancer as a genetically linked disease (Verkasalo et al, 1999). There have been many genes linked with prostate cancer. These include but are not limited to mutations in p53 and retinoblastoma (Skar et al, 1999), MXI 1 gene (Eagle et al, 1995), CAPB, HPC1/rnaSEL, HOC2/ELAC2, HPCX, MSR1, PCAP, and HPC 20 (Nieder et al, 2003). The list of potential candidate genes and their polymorphisms is extensive, but to date none reliably explain the ethnic differences in prostate cancer risk. Many chromosomes have been investigated as candidate regions of prostate cancer. These include but are not limited to 5q, 7q and 19q, which were located in a genome wide linkage analysis to determine prostate cancer aggressiveness (Witte et al, 2000). African-American men experience the highest death rates in prostate cancer, the National Cancer Institute lists the rate as 68.1[1] compared to white males who have a rate of 27.7 (www.cancer.gov/cancertopics). Nieder et al, suggested that African-American ethnicity is a risk factor for developing prostate cancer (Nieder et al, 2003).

High serum levels of the cytokine interleukin 6 [IL-6] have also been correlated with prostate cancer risk (Nakashima et al, 2000). Both prostate cancer explants and human prostate cancer cell lines secrete IL-6 *in vitro* (Nakashima et al, 2000).

This paper will focus on the gene Interleukin 6 Signal Transducer Isoform 1 [IL-6ST], on chromosome 5q11.2, with polymorphisms relating to gp130 [figure 2] in exon 10 [rs 3730293]

[1] Statistics are for 1998-2002 and are adjusted to the 2000 U.S standard million population, and represent the number of deaths per year per 100,000 males.

and exon 14 [rs 3729960]; both single nucleotide polymorphisms [snp] result in an amino acid change.

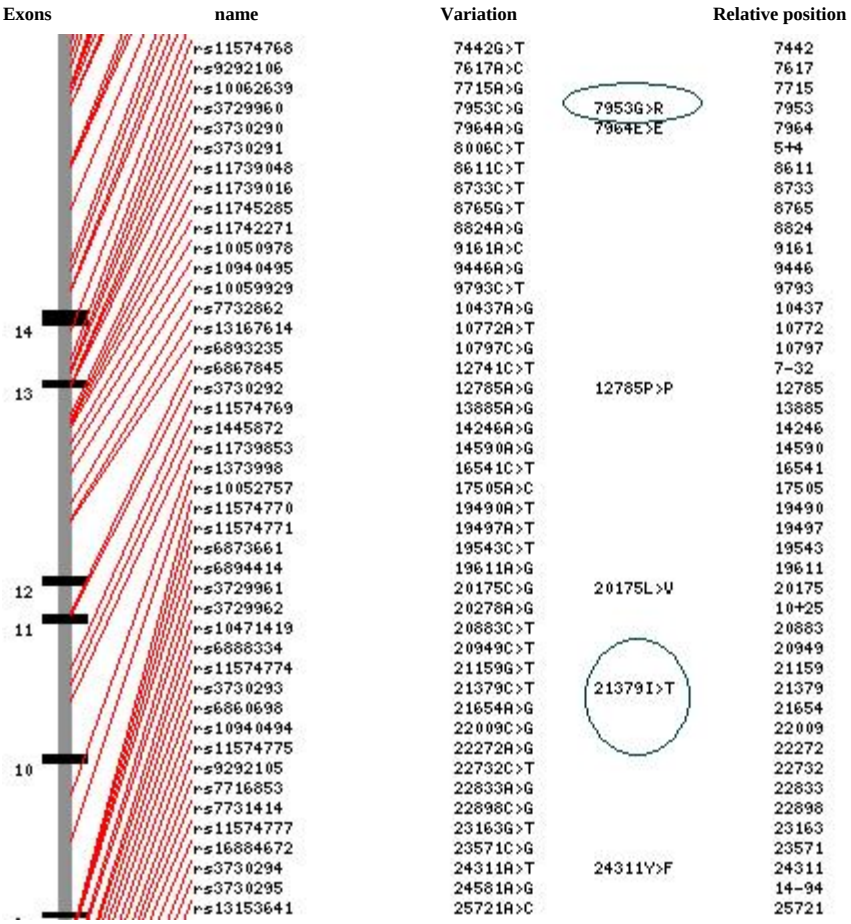


Figure 2: IL6ST gene map and polymorphisms

Figure taken from http://snpper.chip.org/bio/show-gene/15725

These snps were chosen because IL-6 acts through its receptors which are polymorphic, and subsequently may cause it to have different functionality. A complete gene map of the polymorphisms of IL6ST can be found in the appendix. A population based case/control study was conducted to evaluate the influence of gp130 snps on prostate cancer risk in an Afro-Caribbean male population of Tobago.

1.1 INTERLEUKIN 6

Interleukins are cytokines [regulatory proteins secreted by cells] that regulate the interactions between lymphocytes and other leukocytes. They are different from conventional hormones, in that they can have effects on numerous different cells (Tizard). Interleukin 6 [IL-6] can activate target genes involved in survival, differentiation, apoptosis and proliferation (Heinrich et al, 2003). Various types of malignant tumors have implicated IL-6 as being important to their regulation of growth and differentiation; these include renal-cell carcinoma, leukemia and prostate tumors (Lou et al, 2000). Both multiple myeloma and prostate cancer have been attributed to the dysregulation of IL-6 cytokine signaling (Heinrich et al, 2003). In fact, the function of IL-6 as it relates to human malignancy is noticeably established in multiple myeloma, where tumor growth is aided by autocrine stimulation of IL-6 (Giri et al, 2001). Chung and colleagues, suggest IL-6 can be characterized as a paracrine or autocrine growth factor that is implicated in the oncogenic processes of the following tumors: mammary carcinoma, lymphoma, plasmacytoma/myeloma and Kaposi's sarcoma (Chung et al, 1999). IL-6 may induce growth of prostate cancer cells and assist the escape of apoptosis, which would result in an increase in disease development through the augmented production of IL-6. IL-6 is a pleiotropic 21-30kDa glycoprotein consisting of 212 amino acids with varying glycosylation (Chung et al, 1999). It is important to note the single presence of IL-6 is not enough for cell mediation. Human IL-6 signaling requires the 80kDa IL-6R receptor, which is responsible for IL-6 specificity and the 130kDa glycoprotein, gp130, the signal transduction subunit for several cytokines, for signal transduction to occur (Kishimoto et al, 1992). Signal transduction is a process that results in the delivery of an active transcription factor to the cell's nucleus in response to cell surface receptor binding by an extracelluar protein ligand.

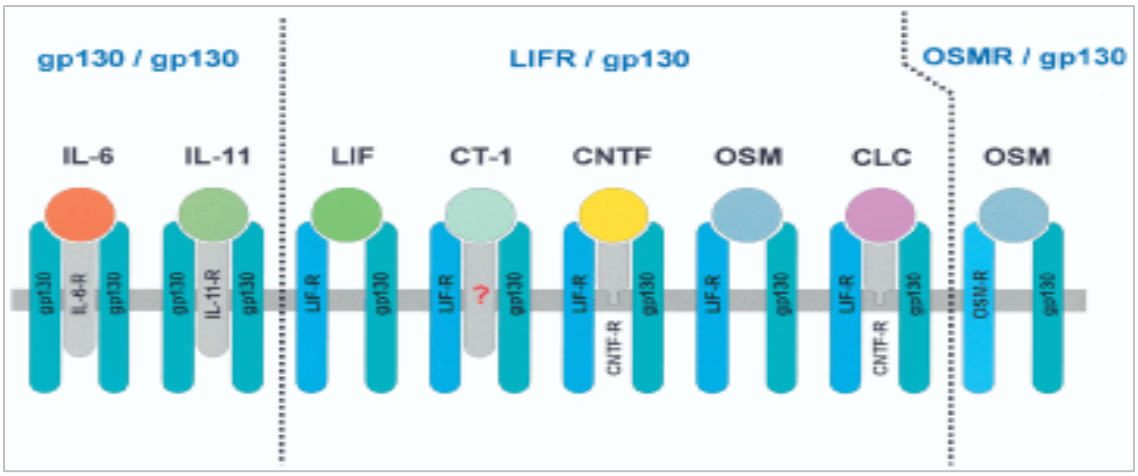


Figure 3: Receptor complexes of IL-6 type cytokines
(Heinrich, 2003)

When IL-6 binds to its receptor IL6-R, it leads to activation of members of the Janus [JAK] kinase family, which in turn phosphorylate tyrosine residues in the cytoplasmic domains of the gp130 subunit. Glycoprotein 130 combines with activators of transcription [STAT factors] to undergo tyrosine phosphorylation, dimerization and translocation to the nucleus (Culig et al, 2002). In the human body gp130 is expressed ubiquitously and all of the IL-6 type cytokine receptor complexes use gp130 as the receptor signaling subunits. These complexes have diverse functions and are involved in immune and inflammation responses, liver and neuronal regeneration, haematopoiesis, fertility and embryonal development (Heinrich et al, 2003). It is interesting to note that gp130 can also transduce signals from many different ligands. For instance, the following all use gp130 as a signal transducer: oncostatin M, leukemia inhibitory factor, cardiotrophin-1, IL-11, ciliary neurotrophic factor, and cardiotrophin-like cytokine (Müller-Newen).

Gp130 is a signal transducer and while it is ubiquitous in the normal human cell, the ability of gp130 to begin signal transduction appears to be regulated by the restricted expression of the ligand binding component. The ligand binding component for IL-6 is IL-6R. For this reason, recent research examining the potential effects of IL-6 on prostate cancer also looks for the presence of IL6R and gp130. The expression of IL-6 and IL-6R has been found in both benign prostate hyperplasia and prostate carcinoma (Lou et al, 2000). In fact both IL-6R and gp130 have been found in four cancer cell lines: hormone dependent LNCaP, and the hormone refractory lines of PC3, DU145 and TSU.

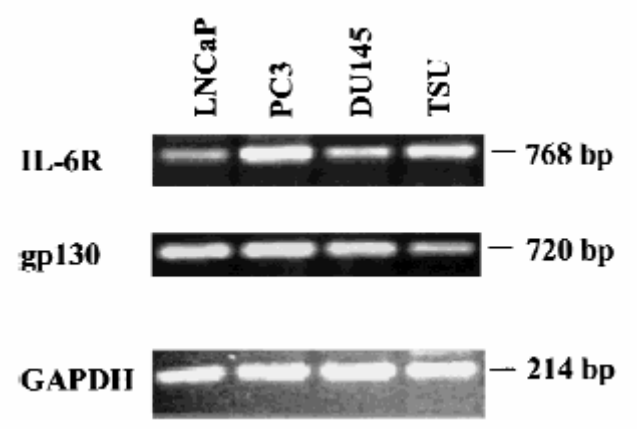


Figure 4: Detection of mRNA expression for both gp 130 and IL-6R by RT-PCR in cell lines (Lou et al, 2000)

The presence of the IL-6 in the LNCaP cancer cell line is controversial. Giri et al, report being unable to detect the secretion of IL-6 from LNCaP (Giri et al, 2001). Chung et al, did not find evidence of IL-6 in the LNCaP cancer cell line and attributed it to "different test conditions" (Chung et al, 1999). However they were able to detect soluble forms of both IL-6R and gp130 by RT-PCR and immunoprecipitation with anti-gp-130 (Chung et al, 1999).

1.2 ANDROGEN INDEPENDENCE

In a normal human prostate epithelial cell, the hormone androgen is responsible for the growth and maintenance of the functional and structural integrity of the cell. The absence of androgen will usually result in apoptosis. Most prostate epithelial cell growth is initially dependent on hormonal stimulation and is therefore androgen-dependent. At this stage, the cells are receptive to androgen-ablative therapies. Androgen-independent prostate cancer cells often escape apoptosis and thrive in the new hormone refractory environment (Chung et al, 1999). In these prostate cancer cells, IL-6 may undergo a functional transition from a paracrine growth inhibitor to an autocrine growth stimulator (Culig et al, 2002).

1.3 HHV-8 AND IL-6

According to Koroidi and colleagues, sexually transmitted infections and sexual history have been discovered to be significant risk factors in the etiology of prostate cancer (Korodi et al, 2005). Among the sexually transmitted viruses is human HHV-8, responsible for the formation of Kaposi sarcoma. HHV-8 is a sexually transmitted, gamma-2 herpesvirus and its presence has been reported in both normal and cancerous prostate tissue (Hoffman et al, 2004). In fact, Hoffman et al, reported an association between prostate cancer and HHV-8 (Hoffman et al, 2004).

The HHV-8 virus includes a functional homologue of interleukin-6 named vIl-6, but unlike IL-6 it does not need the IL-6R subunit to begin signal transduction (Wan et al, 1999). This is important because as previously stated gp130 is ubiquitously expressed in the human

body. In a paper by Wan and colleagues, the activation of STAT1 and STAT3 cells in human HepG2 hepatoma cells by vIL-6 sans its IL-6R was demonstrated (Wan et al, 1999). They also reported that IL-6 is an important autocrine growth factor for Primary Effusion Lymphoma or PEL (Wan et al, 1999). Chung et al characterized IL-6 as either a paracrine or autocrine growth factor that was implicated in the progression of Kaposi sarcoma, it is therefore reasonable to take a closer look at HHV-8 (Chung et al, 1999).

Another paper examined sexually transmitted diseases and prostate cancer risks (Hayes et al, 2000). While they did not look specifically at HHV-8 and prostate cancer risks, the authors did suggest that an infectious agent may act as a co-factor in the development of prostate cancer. HHV-8 could be that co-factor and may act through vIL-6 to increase prostate cancer risk.

MATERIAL AND METHODS

1.4 STUDY POPULATION

Male inhabitants of the island of Tobago were examined for the presence of both prostate cancer and gp130 mutations. Two main islands compose the Republic of Trinidad and Tobago. Tobago is smaller than Trinidad and is located near the southern Caribbean Sea, south of Grenada and northwest of the island of Trinidad (http://en.wikipedia.org/wiki/Tobago). Ninety-two percent of the people who inhabit the Caribbean island of Tobago are self-identified as Afro-Caribbean (Bunker). According to the 1990 Census the population was 46,435 of that 5,121 were males ages 40-79.

1000 DNA samples were genotyped for two single nucleotide polymorphisms. The samples were obtained from the Bunker et al. Tobago study (Bunker 2002). In this study, the male population aged 40-79 of Tobago and Trinidad was solicited for participation in a population based prostate cancer screening survey. The samples were blinded to the researcher and the cancer status of the person was unknown until the time of analysis. In the analysis the samples were broken up into two groups, cases and controls.

1.4.1 CANCER DIAGNOSIS- DISTINCTION BETWEEN CASE AND CONTROL

The clinical diagnosis of subjects with prostate cancer was determined by abnormal DRE's, elevated PSA's and prostate biopsies (Bunker 2002). Initially peripheral blood draws were done and PSA (prostate specific antigen) measurements were taken. The PSA measurements were analyzed at the University of Pittsburgh's Central Pathology Laboratory using the automated Microparticle Enzyme Immunoassay, Abbot AxSYM PSA assay. To avoid artifactual increase in serum PSA, the subjects underwent a DRE (digital rectal exam) at a later date. A physician trained according to the Bunker study protocol performed the digital rectal exam. Subjects with an abnormal DRE or whose serum PSA level was found to be elevated ($\geq$ 4.0 ng/ml) were then selected for biopsy. Pathological evaluation of the prostate tissue was performed by either urologists or surgeons trained by urologists from the University of Pittsburgh's Medical Center. Using an 18 gauge, 21cm spring-loaded biopsy needle, transrectal ultrasound guided biopsies were executed. Sextant biopsies were acquired in accordance with a standard protocol (Bunker 2002). After the evaluations, the men were then labeled as either having prostate cancer or not having prostate cancer. All protocols were both approved and reviewed by the Institutional Review Board of the Tobago Ministry of Health and the University of Pittsburgh. Each participant provided written informed consent. The Bunker et al study found, "The screening detected prevalence of prostate cancer in this Afro-Caribbean population, ages 50-79 years was about three to four times higher than rates reported from screening studies in predominately Caucasian populations." The total screened population presented a prostate cancer prevalence rate of 10.7% among men aged 40-79 (Bunker et al, 2002). The samples used in this paper are a subset of samples from the Bunker study.

1.5 GENOTYPE ANALYSIS

To analyze the PSA levels peripheral blood draws were done. High molecular weight DNA was isolated from the residual clots drawn for PSA tests. Genotype analysis was done by polymerase chain reaction and fluorescence polarization. DNA Engine Dyad and Tetrad 2 machines by Peltier Thermal Cycler were used for the PCR [amplification], SAP [incubation] and TDI [template directed primer extension] steps. Fluorescence polarization analysis was done with a Criterion Host, Analyst HT machine designed by LJL Biosystems.

1.6 POLYMERASE CHAIN REACTION (PCR)

The two single nucleotide polymorphisms chosen were rs 3730293 and rs 3729960. In rs 3730293 the base pair change is **A** to **G** with an amino acid change of Isoleucine to Threonine. In rs 3729960 the base pair change is **C** to **G** with an amino acid change of Leucine to Valine. A total volume of 10μL per reaction composed of water plus the following reagents from Invitrogen: 50 mM $MgCl_2$, 10X PCR Buffer, 5U/μl Taq DNA polymerase, 1.25 mM dNTP and 20μM of forward and reverse primers was used. The primers and conditions are listed in table 1.

Table 1: Primers and Conditions for SNPs

	Primers		Conditions		
	rs 3730293				
Forward	5' CTA GCC AGG TAT ACC TCT 3'	step 1	Initial Denaturation	95 °C	5 minutes
Reverse	5' GCT ACT CAC CCT GTA ATG GAT 3'	step 2	Denaturation	95 °C	30 sec
Detection	5' GAT AAC ACA CAC CAC TCA AGT 3'	step 3	Annealing	47.4 °C	15 sec
		step 4	Extension	72 °C	30 sec
		step 5	Repeat step 2	34 cycles	
		step 6	Final Extension	72 °C	10 minutes
	rs 3729960				
Forward	5' CCA GCA AAA ATG ACT AAC 3'	step 1	Initial Denaturation	95 °C	5 minutes
Reverse	5' GTT GCA TTG TGA ACG AGG 3'	step 2	Denaturation	95 °C	30 sec
Detection	5' CAA GTG TGT TTC CCT TCC AC 3'	step 3	Annealing	55 °C	15 sec
		step 4	Extension	72 °C	30 sec
		step 5	Repeat step 2	34 cycles	
		step 6	Final Extension	72 °C	10 minutes

1.7 FLUORESCENCE POLARIZATION (FP)

The basis for fluorescence polarization is based on the concept of molecular movement and rotation. By using a fluorescent dye to label a small molecule, its subsequent binding to another molecule of equal or greater size can be monitored through its speed of rotation. This process

can determine which allele is present (Chen et al, 1999). There are two steps in FP, the primer/dNTP degradation step with Shrimp Alkaline Phosphatase incubation and the TDI assay where the fluorescent dyes are attached. After dye attachment, the sample was ready for fluorescence polarization measurement (Chen et al, 1999). A total volume of 10μL per reaction composed of water plus the following reagents from Invitrogen: 10x SAP buffer, 1 U/μL SAP and 10 U/μL exonuclease was used.

Table 2: Protocol for SAP step

SAP	conditions	
Incubation	37° C	90 minutes
Denaturation	95° C	15 minutes
Hold	10° C	

After the SAP step gets completed, the TDI assay begins. A total volume of 10μL per reaction composed of water plus the following reagents from Invitrogen: 10x thermosequenase buffer, 10μM internal detection primer, 25 μM dye labeled ddNTP mix, and 4U/μL thermosequenase was used.

Table 3: Protocol for TDI step

TDI	conditions	
Denaturation	94° C	1 minute
Denaturation	94° C	10 sec
Extension	55° C	30 sec
Repeat	Go to step 2	39 cycles
Final Extension	72° C	10 minutes
Hold	10° C	

RESULTS

In a population of men from Tobago who were characterized as having high rates of prostate cancer, two snps in gp 130 were examined and no evidence of association with prostate cancer risk between genotypes or haplotypes was identified. There were 284 cases and 716 controls of which reliable genotypes were obtained for 284 cases and 594 controls in rs 3730293. In rs 3729960, genotypes were obtained for 257 cases and 618 controls.

Failure to genotype was either the result of PCR failure, FP failure or from lack of sufficient DNA. Table 4 shows a summary of observed and expected genotypes for the Tobago male population. A complete list can be found in the appendix section of this paper.

Table 4: Summary of Observed and Expected Genotypes

		284 cases				**716 controls**	
rs 3730293		n= 238				n=594	
		observed	*expected*			*observed*	*expected*
	AA	122	123.58		**AA**	275	283
	AG	99	95.84		**AG**	270	254.01
	GG	17	18.58		**GG**	49	57
wild type	*p*	*0.7206*			*p*	*0.6902*	
	q	*0.2794*			*q*	*0.3098*	
	χ^2	*0.26*			χ^2	*2.35*	
	p-value	*0.61*			*p-value*	*0.12*	
		284 cases				**716 controls**	
rs 3729960		n=257				n=618	
		observed	*expected*			*observed*	*expected*
	CC	66	65.76		**CC**	183	177.28
	CG	128	128.48		**CG**	296	307.43
	GG	63	62.76		**GG**	139	133.28
wild type	*p*	*0.5058*			*p*	*0.5356*	
	q	*0.4942*			*q*	*0.4644*	
	χ^2	*0*			χ^2	*0.85*	
	p-value	*0.95*			*p-value*	*0.36*	

Key to Base Pairs:

A= Wild Type
G= Polymorphism

C=Wild Type
G= Polymorphism

1.8 STATISTICAL ANALYSIS

Hardy Weinberg Equilibrium describes the relationship between allele frequencies and the resulting genotypic frequencies. HWE principles were used to determine the expected number of individuals with each genotype. Allele frequencies were estimated by gene counting. The expected frequencies were then compared to the observed frequencies. The Chi-square test was used to compare the expected allele frequencies to the observed allele frequencies to determine if the loci were in Hardy Weinberg Equilibrium [HWE]. These results can be found in table 4.

The Chi-square test was also used to calculate the homogeneity of the allele or genotype frequencies between the cases and controls. It is used to determine if a significant relationship existed between genotypes of the cases versus genotypes of the controls.

Haploview 3.2 (http://www.broad.mit.edu/mpg/haploview/) was used to calculate if pair wise linkage disequilibrium existed between rs 3729960 and rs 3730293. It can be expressed as D' where D' is a measure of the strength of association between the alleles at the two loci. D' equaling 1 is representative of complete linkage disequilibrium. D' equaling 0 is representative of complete linkage equilibrium. The results can be found in table 6.

1.9 ALLELE FREQUENCIES

In rs 3730293 cases, the wild type allele was represented by "A" coding for the amino acid Isoleucine. Its frequency was 0.7206. The polymorphism was represented by "G" coding for the amino acid Threonine. Its frequency was 0.2794. Both alleles were found to be within HWE with a p-value of 0.61.

In rs 3730293 controls, the wild type allele was represented by “A” coding for the amino acid Isoleucine. Its frequency was 0.6902. The polymorphism was represented by “G” coding for the amino acid Threonine. Its frequency was 0.3098. Both alleles were found to be within HWE with a p-value of 0.12.

In rs 3729960 cases, the wild type allele was represented by “C” coding for the amino acid Glycine. Its frequency was 0.5058. The polymorphism was represented by “G” coding for the amino acid Arginine. Its frequency was 0.4942. Both alleles were found to be within HWE with a p-value of 0.95.

In rs 3729960 controls, the wild type allele was represented by “C” coding for the amino acid Glycine. Its frequency was 0.5356. The polymorphism was represented by “G” coding for the amino acid Arginine. Its frequency was 0.4644. Both alleles were found to be within HWE with a p-value of 0.36.

Table 5: Chi-Square Table for Cases and Controls

rs 3730293

	AA	AG	GG	Total
Cases	122	99	17	238
Controls	275	270	49	594
Total	397	369	66	832

rs3729960

	CC	CG	GG	Total
Cases	66	128	63	257
Controls	183	296	139	618
Total	249	424	202	875

AA & CC represent the wild type alleles

In rs 3730293 no significant relationship was found for the genotypes of the cases compared to those of the controls. The Chi-square value was 1.71 with an insignificant p-value.

In rs 3729960 no significant relationship was found for the genotypes of the cases compared to those of the controls. The Chi-square value was 1.44 with an insignificant p-value.

Table 6: Linkage Disequilibrium Values

Haploview Data	
D'	0.9
LOD	83.19
r-squared	0.357

Linkage Disequilibrium describes a situation in which some combination of AA, AG, GG and CC, CG, GG alleles occur more frequently in the Tobago population than would be expected from this random formation. The Haploview program yielded D' = 0.9 indicating that strong linkage disequilibrium was present for rs 3730293 and rs 3729960 in the Tobago population.

DISCUSSION

Genotype analysis of two polymorphisms in gp130 (rs 3730293 and rs 3729960) in the prostate cancer susceptibility gene IL6ST suggests that the polymorphisms do not significantly contribute to the increased risk of prostate cancer as observed in the case/control population of Tobago. No significant increased or decreased risk for prostate cancer was detected among men carrying the variant genotype. It is worthy to state that the International HapMap Project reports monomorphic allele frequencies for rs3730293[2] in Japanese, Chinese and Utah, U.S populations. Only the Nigerian population presented polymorphic allele frequencies. The Japanese samples were taken from a population in Tokyo, the Chinese samples were taken from a population in Beijing, and the Utah population was composed of residents with ancestry from northern and western Europe. The Ibadan population of Nigeria has allele frequencies very similar to those obtained in this paper. HapMap lists them as the wild type allele **A**=0.617 and the mutated allele **G**= 0.383. The polymorphic nature of these alleles may act in conjunction with other genes or may have different functionality that may have contribute toward prostate cancer risk. The discrepancy in the incidence of prostate cancer according to geographic region and ethnicity is very interesting. Prostate cancer rates in Asian countries are low. In comparison to the United States, countries like Japan and China have prostate cancer rates that are 50-60 times lower (Hsing et al, 2000). Further more the rate of prostate cancer for Caucasians in the United States

[2] No allele frequency information was given for the rs 3729960 polymorphism in either the HapMap database or in the National Center for Biotechnology Information [NCBI] database

is sixty percent less than the rate of African-Americans; although it has been postulated that prostate cancer rates will increase in countries that previously held low rates due to aging populations and increased PSA screening (Hsing et al, 2000).

To find a link to prostate cancer risk it will be necessary to look at more than just the snp's listed in this paper. While it is believed that IL-6 is a good gene to examine for prostate cancer risk, a paper by Sun et al, found some sequence variants of IL-6 that were not associated with prostate cancer risk (Sun et al, 2004). However, those authors did not examine snps relating to glycoprotein 130.

Conflicting research was also found for HHV-8. In a nested case/control study done in Finland by Korodi et al, it was suggested that selection bias may have been present in the Hoffman et al paper. They reported evidence against involvement of both HHV-8 and HSV-2 in prostate carcinogenesis (Korodi et al, 2005).

1.10 FUTURE STUDIES

Prostate Cancer and cancers in general continue to be responsible for illness and death in populations all over the world. Populations with West African ancestry are particularly susceptible to prostate cancer. While the polymorphisms examined in this paper yielded no significant association to prostate cancer, it is important to keep looking. IL-6 has been implicated in a number of studies and more polymorphisms should be identified and researched as potential risks to prostate cancer. It would have been useful to redo this study in another population of men with West African ancestry. The future study should include HHV-8

seroprevalence data and examine more snps in IL6ST particularly looking at functionality with a more detailed haplotype analysis.

CONCLUSION

Research of the two polymorphisms in Interleukin-6 Signal Transducer Isoform 1 did not yield any significant association to prostate cancer risk. While the genotypes were in HWE for all alleles of both the case and control groups, no strong conclusions could be drawn. Further research is needed.

Appendix A

GENOTYPES OF TOBAGO STUDY POPULATION

ID Number	PC status	rs 3729960	rs3730293		ID Number	PC status	rs 3729960	rs3730293
TP970002CJ	control	**CG**	**AA**		TP991123VP	control		**AG**
TP970008DP	control	**GG**	**AG**		TP991125DM	case	**CG**	**AA**
TP970009HP	control	**CG**	**AG**		TP991127AM	control	**GG**	**AA**
TP970013LM	case	**GG**	**AG**		TP991137WF	case	**GG**	**GG**
TP970014PB	control	**CC**	**AA**		TP991139EC	control	**CC**	**AA**
TP970017CG	control	**GG**	**GG**		TP991140JB	case	**GG**	**AG**
TP970022DH	case	**CC**			TP991143SR	case	**GG**	**AG**
TP970024JM	control	**CC**	**AA**		TP991146AT	control		**AA**
TP970025WR	control	**CG**	**AG**		TP991148AR	control	**CC**	
TP970028VR	control	**CC**	**AA**		TP991149JW	control	**CG**	**AG**
TP970029HA	control	**CC**			TP991150CB	control		**AA**
TP970030ME	control	**CG**	**AG**		TP991152AT	control	**CC**	**AA**
TP970033FG	control	**CG**	**AG**		TP991155RS	control	**CC**	
TP970035AM	case	**CC**	**AA**		TP991159AA	control	**CG**	**AA**
TP970037FC	control	**GG**	**AG**		TP991163EA	control	**GG**	**AG**
TP970040AP	control	**CG**	**AG**		TP991166CN	case	**CG**	**AA**
TP970042WR	control	**CG**	**AG**		TP991170GK	control	**CG**	**AG**
TP970043NH	control	**CC**	**AA**		TP991181MC	control	**CG**	**AG**
TP970045FD	control	**GG**	**AG**		TP991182GD	control	**GG**	**AG**
TP970046RH	case	**CG**	**AA**		TP991186CB	control	**CC**	
TP970048PR	case	**GG**	**AG**		TP991188CS	case	**GG**	**AG**
TP970049PP	case	**CC**	**AA**		TP991191LJ	case	**CG**	**AG**
TP970052OD	case	**GG**			TP991195GS	control	**CG**	**AA**
TP970053SD	control	**CG**			TP991196VR	control	**GG**	**AG**
TP970054LR	control		**AA**		TP991197MD	case	**GG**	**AG**
TP970056WT	control	**CG**	**AG**		TP991198WB	case	**GG**	**AA**
TP970058HE	control	**CC**	**AA**		TP991199BC	control	**CG**	**AG**
TP970059GW	control	**CG**	**AG**		TP991200OB	case	**CC**	**AA**

TP970060LC	control	**CC**	**AA**		TP991204JA	control	**CG**	**AA**
TP970061JL	control	**GG**	**AG**		TP991205ST	control	**CG**	**AG**
TP970063HP	control	**CG**	**AG**		TP991207HR	control	**CG**	**AA**
TP970064AD	control		**GG**		TP991208EB	control	**GG**	**AA**
TP970065GR	control	**CC**	**AA**		TP991209EA	control	**CG**	**AA**
TP970066LC	control	**CG**	**AA**		TP991210WG	case	**CG**	**AA**
TP970067CL	control	**CG**	**AA**		TP991211LT	control	**GG**	**AG**
TP970068CN	case	**CG**	**AA**		TP991215CB	control	**CG**	**AG**
TP970069GA	control	**GG**	**AG**		TP991217OB	control	**CG**	**AG**
TP970071EA	control	**CG**	**AG**		TP991219RJ	control	**CC**	**AA**
TP970077AR	case	**CG**	**AA**		TP991221KG	control	**CC**	**AA**
TP970078JR	control	**CG**	**AG**		TP991224JR	case	**CC**	**AA**
TP970079RM	control	**CC**	**AA**		TP991225RS	case	**CG**	**AG**
TP970080AS	control	**CG**	**AG**		TP991227EC	control	**CC**	**AA**
TP970082RJ	case	**CG**	**AA**		TP991230HS	control	**CG**	**AG**
TP970083RA	control	**CC**	**AA**		TP991233WW	control	**CG**	**AA**
TP970084HG	case	**CG**	**AG**		TP991234RL	case	**GG**	**AG**
TP970085SS	control	**CG**	**AA**		TP991235UG	case	**CC**	**AA**
TP970086GT	case	**CC**	**AA**		TP991237SG	control	**CG**	**AG**
TP970087HL	control	**GG**	**GG**		TP991242RD	control	**CG**	**AA**
TP970088ED	control	**CC**	**AA**		TP991243RM	control	**CC**	**AA**
TP970089ED	control	**CG**			TP991244GP	control	**CG**	**AA**
TP970090JR	case	**CC**	**AA**		TP991245AB	control	**GG**	**AA**
TP970091AM	case	**CG**	**AG**		TP991246MJ	control	**CG**	**AG**
TP970094SB	control	**GG**	**AA**		TP991249JT	control		**AA**
TP970095ND	control	**CC**	**AA**		TP991250AB	control	**CC**	**AA**
TP970097CT	control	**CC**	**AG**		TP991255RQ	control	**CG**	**AG**
TP970098AT	case	**GG**	**GG**		TP991259NS	control	**CG**	**AG**
TP970099RS	control	**CG**	**AG**		TP991260CJ	case	**CG**	**AA**
TP970103DM	case	**GG**	**AG**		TP991263DD	control		**AA**
TP970106WC	control	**GG**	**AG**		TP991267FS	case		**AA**
TP970107CD	control	**CG**	**AG**		TP991269AB	control	**GG**	**AG**
TP970108JR	control	**CC**	**AA**		TP991273AF	control	**CG**	**AA**
TP970109TP	case	**CG**	**AG**		TP991274EJ	case	**CG**	**AG**
TP970112OS	case	**CC**	**AA**		TP991276NR	control	**CG**	**AA**
TP970113HT	control	**CC**			TP991278SB	control	**GG**	**AG**
TP970115EM	control	**CG**	**AG**		TP991283HE	control	**CC**	**AA**
TP970119CA	case	**CG**	**AG**		TP991284PJ	control	**CC**	**AA**
TP970123VW	control	**CG**	**AA**		TP991286CP	control	**CG**	**AG**
TP970126RC	control	**CG**	**AG**		TP991289DB	control	**CG**	**AA**
TP970127EP	control		**AA**		TP991290LK	case	**CG**	**AG**
TP970130FK	control	**CC**	**AA**		TP991291LT	case	**GG**	**AA**
TP970132KM	control	**CG**			TP991292CP	control	**GG**	**AG**
TP970134JG	control	**GG**	**AA**		TP991293UL	control		**AG**

TP970135HC	control	**CG**	**AG**		TP991296LT	case	**GG**	**AA**
TP970137HO	control	**CG**	**AG**		TP991301SR	control	**CG**	**AG**
TP970138FP	control	**CG**	**AG**		TP991303CC	control	**CG**	
TP970139GP	control	**CG**	**AA**		TP991305BC	control	**CG**	**AG**
TP970140DS	case	**GG**	**GG**		TP991306SP	control	**CC**	**AA**
TP970141AR	control	**GG**	**AG**		TP991307LS	control	**CG**	**AA**
TP970145VD	control	**CG**			TP991308PJ	control	**CG**	**AG**
TP970146SD	control	**GG**	**GG**		TP991309KW	control	**CC**	**AA**
TP970151AC	control	**GG**	**AG**		TP991312WD	control	**CG**	
TP970152AT	control	**CG**	**AG**		TP991318CS	control	**CG**	**AG**
TP970153NB	control	**CG**	**AG**		TP991319LA	control	**CC**	**AA**
TP970155CW	control	**CG**	**AG**		TP991325CP	control	**CC**	**AA**
TP970158CC	control	**GG**			TP991326DL	control	**CG**	**AG**
TP970160GG	case	**CG**	**AA**		TP991330AD	control	**GG**	**GG**
TP970161JD	control	**CG**	**AG**		TP991331RC	case	**CG**	**AA**
TP970162IL	control	**GG**	**GG**		TP991339SG	case	**CG**	**AG**
TP970163JQ	control	**CG**	**AG**		TP991340DW	case	**GG**	
TP970165CO	case	**CC**	**AG**		TP991346HB	control	**GG**	**AA**
TP970167CB	case	**CG**	**AA**		TP991348GB	control	**CC**	**AA**
TP970169LG	case	**CG**	**AG**		TP991352HM	control	**GG**	**AG**
TP970170FR	control	**CG**	**AG**		TP991356RM	control	**CG**	**AG**
TP970171JW	control	**GG**	**AG**		TP991357CH	control	**CG**	**AG**
TP980173CI	control	**CG**	**AG**		TP991359SC	case	**GG**	**GG**
TP980180WJ	control	**CG**	**AA**		TP991362HB	control	**CG**	**AA**
TP980182WW	case	**CC**	**AA**		TP991366JM	case	**CG**	**AG**
TP980184JM	case	**GG**	**AA**		TP991367CM	case	**GG**	**GG**
TP980185PJ	control	**CG**	**AG**		TP991370KC	control	**GG**	**GG**
TP980187AC	control	**CG**	**AA**		TP991372MJ	case	**GG**	**AG**
TP980188AJ	control	**CC**	**AA**		TP991377DP	control	**CG**	**AA**
TP980189MG	control	**GG**	**AA**		TP991378DS	control	**CC**	**AA**
TP980193CP	control	**CC**	**AA**		TP991379SA	control	**CC**	**AA**
TP980194CR	case	**CG**	**AA**		TP991384AF	case	**CG**	
TP980195FD	control	**CC**	**AA**		TP991385HB	control		**AG**
TP980198JQ	control	**CG**	**AG**		TP991389CG	case	**GG**	**AA**
TP980199HW	control	**GG**	**GG**		TP991392TB	case		**AG**
TP980200HJ	control	**CC**	**AA**		TP991397SB	control	**GG**	
TP980201LC	case	**CC**	**AA**		TP991398LH	control	**CC**	
TP980202WP	control	**CC**	**AA**		TP991402MT	control	**GG**	**GG**
TP980206CC	control	**CG**	**AG**		TP991405AT	case	**CG**	**AG**
TP980207NF	control	**CG**	**AG**		TP991406RS	case	**CC**	**AA**
TP980210CT	control	**CC**	**AA**		TP991408MC	case	**CG**	**AG**
TP980212SD	control	**CC**	**AA**		TP991411DL	control	**GG**	**AG**
TP980214HL	control	**CG**	**AG**		TP991412EC	case	**CG**	**AA**
TP980217HP	control	**CC**	**AA**		TP991419PG	control	**GG**	

TP980218AD	case	**CC**	**AA**		TP991423CJ	case	**GG**	**AG**
TP980221WR	control	**CC**	**AA**		TP991424IA	control	**GG**	**GG**
TP980222HC	control	**GG**	**AG**		TP991427BP	control	**CG**	**AG**
TP980224NM	control	**CC**	**AA**		TP991439JP	case		**AA**
TP980225VS	control	**GG**	**AG**		TP991440NT	case	**CC**	
TP980226AJ	control	**CC**	**AG**		TP991441VB	control	**GG**	**AG**
TP980227IA	control	**CC**	**AA**		TP991442WC	case	**CG**	**AG**
TP980228WA	control	**CC**	**AA**		TP991447KT	control	**CG**	**AG**
TP980230SC	case	**CC**	**AA**		TP991449DL	control	**GG**	**AG**
TP980233KC	control	**CC**	**AA**		TP991455EW	case	**GG**	**AA**
TP980234AB	control	**CC**	**AG**		TP991456TM	control	**CG**	**AG**
TP980235MW	case	**CC**	**AA**		TP991463RW	control	**GG**	**GG**
TP980241ET	control	**CC**	**AA**		TP991466MT	control		**AA**
TP980250NB	control	**GG**	**AG**		TP991467GR	control		**AA**
TP980252KS	control	**CC**	**AA**		TP991475DQ	control	**CG**	**AG**
TP980254HA	case	**CG**	**AG**		TP991490FJ	control	**CC**	**AA**
TP980258RE	control	**CC**	**AA**		TP991495HP	control	**GG**	
TP980262RH	control	**GG**	**AG**		TP991496EG	control	**CG**	**AG**
TP980263AW	case	**CC**	**AA**		TP991497AB	case	**CG**	
TP980264AT	control	**CC**			TP991500RO	control	**GG**	
TP980265DP	control		**AG**		TP991506HA	control	**GG**	
TP980266CT	control	**CG**	**AG**		TP991510ES	control	**GG**	**AG**
TP980269SC	control	**CC**	**AG**		TP991514KK	case	**CG**	
TP980271JM	control	**CG**	**AG**		TP991515CF	control	**CG**	**AG**
TP980272TR	case	**GG**	**AG**		TP991518TB	control		
TP980276JJ	control	**CG**			TP991521MK	case		
TP980280FC	control	**CG**	**AA**		TP991522JW	control		
TP980281FS	case	**GG**	**AG**		TP991525AB	control		
TP980282TJ	case	**CG**	**AA**		TP991526IH	case		
TP980283JG	control	**CC**	**AA**		TP991534KN	control		
TP980287GJ	control	**CC**	**AA**		TP991539ES	control		
TP980289LP	case	**CG**	**AG**		TP991542WR	control		
TP980292NG	control	**CG**	**AA**		TP991545LN	control		
TP980293HT	case	**CC**	**AA**		TP991553EP	control		
TP980297JM	control	**CC**	**AG**		TP991557HJ	case		
TP980298DA	control	**CG**	**AA**		TP991559HL	control		
TP980307CE	control	**CC**	**AA**		TP991565HG	control		
TP980309CD	control	**GG**	**AG**		TP991581BD	control		
TP980310AT	case	**CC**	**AA**		TP991584FC	control		
TP980313JG	control	**CG**	**AG**		TP991587DW	control		
TP980322JM	control	**CC**	**AA**		TP991588AJ	case		
TP980323SB	case	**CC**	**AA**		TP991592AT	control		
TP980324TL	control	**CC**	**AA**		TP991594LG	control		
TP980329TS	control	**CC**	**AA**		TP991599HB	control		

TP980331AP	control	**CG**	**AG**		TP991601EN	control		
TP980332LB	case	**GG**	**AG**		TP991604RP	control		
TP980334WA	case	**CG**	**AA**		TP991605IP	control		
TP980336ET	control	**CG**			TP991607DH	control		
TP980337DD	control	**CC**	**AA**		TP991612CA	control		
TP980339DC	control	**CC**	**AA**		TP991615NC	control		
TP980341PP	case	**CG**	**AG**		TP991618JL	case		
TP980342RG	control	**CG**	**AG**		TP991619EP	control		
TP980346JJ	control	**CC**	**AG**		TP991621RJ	control		
TP980348JA	control	**GG**	**AG**		TP991628VT	case		
TP980350SP	control	**CC**	**AA**		TP991631CC	control		
TP980351FJ	control	**CC**	**AA**		TP991632CP	control		
TP980354AP	control	**CG**	**AA**		TP991633DD	control		
TP980357HH	control	**GG**	**AG**		TP991634HJ	control		
TP980358AP	control	**CC**	**AA**		TP991638IC	control		
TP980360SW	case	**GG**	**AG**		TP991644CM	control		
TP980361CC	control	**CG**	**AA**		TP991645EM	case		
TP980367JR	control	**GG**	**AG**		TP991649FM	control		
TP980370WG	control	**CG**	**AG**		TP991651CD	control		
TP980372NA	control	**CG**	**AA**		TP991655GD	control		
TP980377JT	control	**GG**			TP991656RC	case		
TP980378GH	control	**CG**	**AA**		TP991663PD	control		
TP980381GB	case	**CG**	**AA**		TP991664NM	control		
TP980382HT	control	**CC**	**AA**		TP991668GD	control		
TP980383AM	case	**CC**	**AA**		TP991673WM	control		
TP980385TB	case	**GG**	**AG**		TP991679KT	control		
TP980387SM	control	**CC**	**AG**		TP991688OW	control		
TP980388HP	control	**CC**	**AA**		TP991699ST	control		
TP980391DJ	control	**GG**	**AA**		TP991719TS	control		
TP980393LA	control	**CG**	**AG**		TP991720PC	control		
TP980395HJ	control	**CC**	**AA**		TP991721GM	control		
TP980396JS	control	**CG**	**AA**		TP991722RD	control		
TP980398PW	control	**CG**	**AA**		TP991725SH	control		
TP980401HS	case	**CG**	**AA**		TP991729CM	control		
TP980405VC	control	**CC**	**AA**		TP991737IA	control		
TP980406HC	case	**CC**	**AA**		TP991738LM	control		
TP980407SC	control	**CG**	**AG**		TP991741WR	control		
TP980408JW	control	**CG**	**AG**		TP991743CR	control		
TP980410DP	control	**CG**	**AG**		TP991751PJ	control		
TP980412JJ	control	**CC**	**AA**		TP991756EA	control		
TP980413LW	case	**GG**	**GG**		TP991761TH	control		
TP980416CH	control	**GG**	**AG**		TP991762SB	control		
TP980422MM	control	**CG**	**AA**		TP991795AJ	control		
TP980423SW	control	**CG**	**AG**		TP991807AL	control		

TP980424LJ	control	**CC**	**AA**		TP991809BA	control	**CG**	
TP980425SF	control	**CG**	**AG**		TP991869MQ	case	**CC**	**AA**
TP980427JD	case	**CC**	**AA**		TP991897JL	control	**GG**	**AG**
TP980429JH	control	**CG**	**AG**		TP991901ML	control	**CG**	**AA**
TP980431JR	control	**CG**	**AG**		TP991902VG	case	**CC**	
TP980433RD	control	**GG**	**AG**		TP991912RE	control	**CC**	**AG**
TP980434GP	control	**CG**	**AA**		TP991916JL	control	**CC**	**AA**
TP980435CJ	control	**CG**	**AG**		TP991917TM	case	**CG**	
TP980436SS	control	**GG**	**GG**		TP991918JM	case	**CG**	**AA**
TP980437TJ	control	**CG**	**AG**		TP991939WK	case	**CG**	
TP980438JP	control		**AA**		TP991947GC	control	**CC**	**AA**
TP980440GB	case	**CG**	**AA**		TP991952CM	control	**GG**	**AG**
TP980442ET	control	**CG**	**AG**		TP991959GH	control	**CC**	**AA**
TP980444HA	case	**CG**	**AA**		TP991963HS	control	**CG**	**AA**
TP980446DB	case	**CC**	**AA**		TP991974LQ	control	**CG**	**AA**
TP980447HM	case	**CG**	**A**		TP991979JP	control	**CG**	**AA**
TP980448LD	control	**CC**	**AA**		TP991980TC	control	**GG**	**AA**
TP980449MJ	case	**CC**	**AA**		TP991990TR	case		**AA**
TP980450CR	control	**CG**	**AA**		TP991997ED	case	**CG**	**AG**
TP980453HD	control	**GG**	**GG**		TP992002VK	case	**CG**	**AG**
TP980454HW	case	**CG**	**AG**		TP992007CK	case	**CG**	
TP980458CM	control	**GG**	**AG**		TP992009WM	case	**GG**	
TP980460UC	control	**CG**	**AA**		TP992012RB	control	**GG**	**AG**
TP980461JE	control		**GG**		TP992022MB	case	**CC**	
TP980467CP	control	**CC**	**AA**		TP992023SC	control	**CG**	**AG**
TP980468PJ	case	**CG**	**AG**		TP992036CS	case	**CG**	**AA**
TP980476AG	case	**GG**	**AG**		TP992041RJ	control	**CG**	**AG**
TP980485BA	case	**CG**	**AG**		TP992043LT	control	**CC**	**AG**
TP980486IL	control	**GG**	**GG**		TP992045TG	control	**GG**	**GG**
TP980488KA	control	**CG**	**AA**		TP992047GK	control	**CG**	**AG**
TP980490AJ	control	**CG**	**AG**		TP992048AL	control	**CG**	**AG**
TP980492CE	control	**GG**	**AG**		TP992050CS	control	**CG**	
TP980497RB	case	**CC**	**AA**		TP992051CJ	control	**GG**	**AG**
TP980498ST	control	**CC**	**AA**		TP992056MP	case	**CG**	**AA**
TP980499LQ	case	**CC**	**AA**		TP992058GA	case	**CG**	**AG**
TP980500IT	case	**CG**	**AG**		TP992060SM	control	**GG**	**AG**
TP980501LJ	control	**CG**	**AG**		TP992061ED	control	**CC**	**AA**
TP980502WP	control	**CC**	**AA**		TP992062CG	case	**CG**	**AA**
TP980503CG	control	**CG**			TP992063ED	case	**CG**	**AG**
TP980506WJ	case	**CG**	**AG**		TP992064AT	control	**CC**	**AA**
TP990508OC	control	**CC**	**AA**		TP992071NB	case	**GG**	**AG**
TP990509DG	case	**CC**	**AA**		TP992072LB	case	**GG**	**AA**
TP990510PA	control	**CG**	**AG**		TP992073VC	control	**CG**	**AA**
TP990512HK	case	**CC**	**AA**		TP992075AM	control	**CG**	**AG**

TP990517GH	case	**CG**	**AG**		TP992078BP	control		**AA**
TP990518FC	case	**GG**	**GG**		TP992084GF	case	**CG**	
TP990522HM	control	**CG**	**AG**		TP992087DW	case	**CG**	
TP990523GS	case	**CC**	**AA**		TP992095GB	case	**CG**	
TP990524SR	control	**CG**	**AA**		TP992097DR	control	**CC**	**AA**
TP990526JO	control	**CG**	**AG**		TP992101LS	case	**CG**	**AG**
TP990528JG	control	**CC**	**AA**		TP992147DT	case	**GG**	**AG**
TP990530OD	case	**GG**	**AG**		TP992158TP	control	**GG**	**AG**
TP990532LV	control	**CC**	**AA**		TP992165EW	case	**GG**	
TP990537CA	case	**CG**	**AG**		TP992167CW	case	**GG**	
TP990538RJ	control	**CG**	**AG**		TP992191AR	control	**CG**	**AG**
TP990540OM	control	**CG**			TP992195EP	control	**CG**	**AG**
TP990541IJ	control	**CG**	**AG**		TP992204SC	case	**CG**	
TP990542OA	control	**CG**	**AG**		TP992207WA	control	**CG**	**AA**
TP990549CB	control	**CG**	**AA**		TP992208WC	case	**CG**	
TP990551IC	control	**GG**	**AG**		TP992209RS	control	**CG**	**AA**
TP990552SP	control	**CC**	**AA**		TP992212MN	control	**CG**	
TP990553ER	control	**GG**	**AG**		TP992214HC	case	**GG**	
TP990555LA	control				TP992228MC	control	**CG**	**AA**
TP990561CC	control	**CG**	**AA**		TP992233CR	case	**CC**	
TP990562GW	case	**CC**	**AA**		TP992241CH	control	**GG**	**AA**
TP990563VS	control	**CC**	**AA**		TP992242FS	case	**CC**	**AA**
TP990564DB	control	**CG**	**AG**		TP992246RC	case	**CG**	**AG**
TP990565CM	control	**CG**	**AG**		TP992260DK	control	**CG**	**AG**
TP990566PS	control	**CC**	**AA**		TP992267EB	control	**CC**	**AG**
TP990568VJ	control				TP992275DT	case	**CG**	**AA**
TP990572AC	control	**CG**	**AG**		TP992281RD	case	**GG**	**AA**
TP990573CG	case	**CG**	**AG**		TP992295JB	control	**CG**	**AA**
TP990574BL	control	**CG**	**AA**		TP992297SB	case	**CC**	
TP990575FM	control	**GG**	**GG**		TP992303ET	control	**CC**	**AA**
TP990576VJ	control	**CG**	**AA**		TP992306EG	case	**CC**	**AA**
TP990577NL	control	**CG**			TP992308KG	control	**GG**	**GG**
TP990578AM	control	**GG**	**GG**		TP992309GB	control	**GG**	**AA**
TP990579NM	control	**CG**	**AA**		TP992313ED	control	**CC**	**AG**
TP990581LK	case	**GG**	**GG**		TP992316HL	control	**CC**	**AG**
TP990582EA	control	**CG**	**AA**		TP992317EA	control	**CC**	**AA**
TP990584CB	case	**CG**			TP992323HC	case		**AA**
TP990585SD	control	**CG**	**AA**		TP992341CJ	case	**GG**	
TP990586JJ	case	**CG**	**AG**		TP992346ES	control	**CG**	**AA**
TP990589JP	case		**GG**		TP992359NS	case	**CG**	**AA**
TP990591CT	control	**CG**	**AG**		TP992360HW	control	**CG**	
TP990595AM	control	**CG**	**AG**		TP992366SS	control	**GG**	**AA**
TP990598AJ	control		**AA**		TP992377JJ	control	**CG**	**AG**
TP990602AD	control	**GG**			TP992379KJ	case	**CG**	**AA**

TP990603RM	control	**CG**	**AG**		TP992381ET	control	**GG**	**AG**
TP990604KR	control	**GG**	**GG**		TP992387JA	control	**CC**	**AA**
TP990605SD	control	**CG**	**AA**		TP992389CW	control	**GG**	**AA**
TP990607JS	control	**CG**	**AG**		TP992392AC	control	**CC**	**AG**
TP990608BI	control	**CG**	**AG**		TP992395WH	control	**GG**	**GG**
TP990609CH	control	**CC**	**AA**		TP992396RP	control	**CG**	**AG**
TP990611SG	control	**CC**	**AA**		TP992397JG	control	**CG**	**AG**
TP990612CF	control	**CC**	**AA**		TP992403LB	control	**CG**	
TP990616EF	case	**CC**	**AA**		TP992406JM	control	**CC**	**AG**
TP990617ES	case	**CG**	**AG**		TP992407EG	control	**CG**	**AA**
TP990618SR	control	**CG**	**AA**		TP992414TC	control	**GG**	**AG**
TP990619CB	control	**CG**	**AG**		TP992420KW	control		**AG**
TP990623AR	case	**GG**	**AG**		TP992431CW	control	**GG**	**GG**
TP990624CJ	control	**CG**	**AA**		TP992433AK	control	**CG**	**AG**
TP990625HR	case	**GG**	**GG**		TP992439VN	case		**AA**
TP990626SM	control	**CC**	**AA**		TP992441HJ	control	**CC**	**AA**
TP990630FD	control	**GG**	**AG**		TP992442CK	control	**CC**	**AG**
TP990631JJ	control	**CG**			TP992444AG	control	**CG**	**AG**
TP990632CK	control		**AA**		TP992446DW	control	**CG**	**AG**
TP990633MA	case	**CC**	**AA**		TP992455TW	control	**GG**	**GG**
TP990634CG	control	**CG**	**AA**		TP992456HQ	control	**GG**	**AG**
TP990635AS	control	**CG**	**AA**		TP992459RG	case	**CG**	**AA**
TP990636FK	control	**CG**	**AA**		TP992460FK	control	**CG**	**AA**
TP990637JW	control	**CG**	**AG**		TP992461CR	control	**CG**	**AA**
TP990638LS	control	**CC**	**AA**		TP992462JD	control	**GG**	**AG**
TP990641MD	control	**CG**	**AA**		TP992463OT	control		**GG**
TP990643DB	case	**CG**	**AA**		TP992465TF	case	**CC**	**AA**
TP990645AB	control	**CC**	**AA**		TP992470NH	control	**GG**	**AG**
TP990646NG	control	**GG**	**GG**		TP992471LM	control	**CG**	**AA**
TP990649MW	control	**CG**			TP992472PT	control		**AA**
TP990650BS	control	**CC**	**AA**		TP992475WS	case	**CC**	**AA**
TP990651JA	control	**GG**	**GG**		TP992476PD	case	**CC**	**AA**
TP990654CH	case	**CG**	**AA**		TP992477GC	case	**CG**	**AG**
TP990655HS	control	**CG**	**AG**		TP992479WB	case	**CC**	**AA**
TP990656ER	control	**CG**	**AG**		TP992482IB	control	**CG**	**AA**
TP990657BH	case	**CG**	**AA**		TP992485JG	control	**CG**	**AG**
TP990658JA	control	**CG**	**AA**		TP992488CW	control	**GG**	**GG**
TP990659GW	control		**AA**		TP992489AC	control	**CG**	**AA**
TP990660KW	control	**CG**	**AG**		TP992491CA	control	**CC**	**AA**
TP990661RM	control	**GG**	**GG**		TP992492MM	control	**CC**	**AA**
TP990662CJ	control	**CC**	**AA**		TP992493AB	control		**AG**
TP990663AH	control	**CC**	**AA**		TP992495JA	control	**GG**	**AA**
TP990665DS	control	**GG**	**AG**		TP992497NP	control	**CC**	**AG**
TP990666WS	case				TP992498IB	case	**CG**	

TP990670WW	control	**CG**	**AG**		TP992532EC	case	**GG**	**GG**
TP990671ER	control	**CG**	**AG**		TP992576AA	control		**GG**
TP990672JB	control		**AA**		TP992579AS	control	**GG**	**AA**
TP990673AT	control		**AG**		TP992581HM	control	**CG**	
TP990678VA	control	**CG**	**AG**		TP992582RD	control	**GG**	**GG**
TP990679BF	case	**CG**	**AG**		TP992592LT	control	**GG**	**AG**
TP990680LP	control	**GG**	**GG**		TP992595EC	control	**CG**	
TP990682TS	case	**CG**	**AA**		TP992598MC	control	**GG**	**GG**
TP990686FC	case	**GG**	**GG**		TP992599VO	control	**CG**	**AA**
TP990687LT	case	**CC**	**AA**		TP992601JD	control	**CG**	
TP990689AJ	control	**CG**	**AA**		TP992603JN	control	**CG**	**AG**
TP990690FW	control	**CC**	**AA**		TP992606ME	control	**CG**	**AA**
TP990694SJ	control	**CG**			TP992612HP	control		**AG**
TP990695EW	case	**CC**	**AA**		TP992618HC	control	**CC**	**AG**
TP990696CW	control	**CC**	**AA**		TP992622BW	control	**CG**	**AG**
TP990697AH	case	**GG**	**AG**		TP992623BW	control	**CC**	**AG**
TP990698EM	control	**CC**	**AA**		TP992624LW	case	**CG**	**AA**
TP990699GH	control	**CC**	**AA**		TP992628KB	control	**CG**	**AA**
TP990703TP	case	**GG**	**AA**		TP992631FB	case	**CC**	**AA**
TP990710NC	case	**CG**	**AG**		TP992633BL	case	**CG**	**AA**
TP990713JT	case	**CG**	**AA**		TP992634BO	control	**CG**	**AG**
TP990714CB	control	**GG**	**AG**		TP992636MG	control	**CG**	**AG**
TP990715HA	control	**CC**	**AA**		TP992637WM	control	**CC**	**AG**
TP990719OP	control	**CG**	**AG**		TP992640CD	control	**CG**	**AG**
TP990722FM	control	**CC**	**AA**		TP992641CW	control	**CC**	**AA**
TP990723HD	case	**CC**	**AA**		TP992644RM	control	**GG**	**AG**
TP990727SC	control		**AG**		TP992645SW	case	**CG**	**AG**
TP990731HS	control	**CC**	**AA**		TP992650NC	case		**AG**
TP990733TH	control	**CC**	**AA**		TP992701NP	control	**CG**	**AG**
TP990735AC	case	**CG**	**AG**		TP992704KM	control	**GG**	**AA**
TP990740AH	case	**CC**	**AA**		TP992707SW	control	**GG**	**AG**
TP990741DH	control	**CC**	**AA**		TP992708AW	control	**CG**	**AG**
TP990742AS	control	**CG**	**AG**		TP992709RW	control	**GG**	**AA**
TP990744UK	control				TP992710FW	control		**AA**
TP990747JR	control	**CG**	**AG**		TP992717AM	control	**CC**	**AA**
TP990748CB	control	**CG**	**AG**		TP992719BM	case	**CC**	**AA**
TP990749RJ	control	**CG**			TP992722CS	control	**GG**	**AA**
TP990751LM	control	**CG**	**AA**		TP992724CP	control	**CC**	**AG**
TP990752MW	case	**GG**	**GG**		TP992725LT	case	**CG**	**AA**
TP990754DS	control	**CG**	**AA**		TP992728AA	control	**CC**	**AA**
TP990757MN	case	**CC**	**AA**		TP992732UD	case		**AA**
TP990761MB	case	**CG**	**AG**		TP992741FR	case		**AG**
TP990773RF	case	**CG**	**AG**		TP992770GW	control	**CC**	**AA**
TP990774NF	control	**CC**	**AA**		TP992779TJ	control	**CC**	**AA**

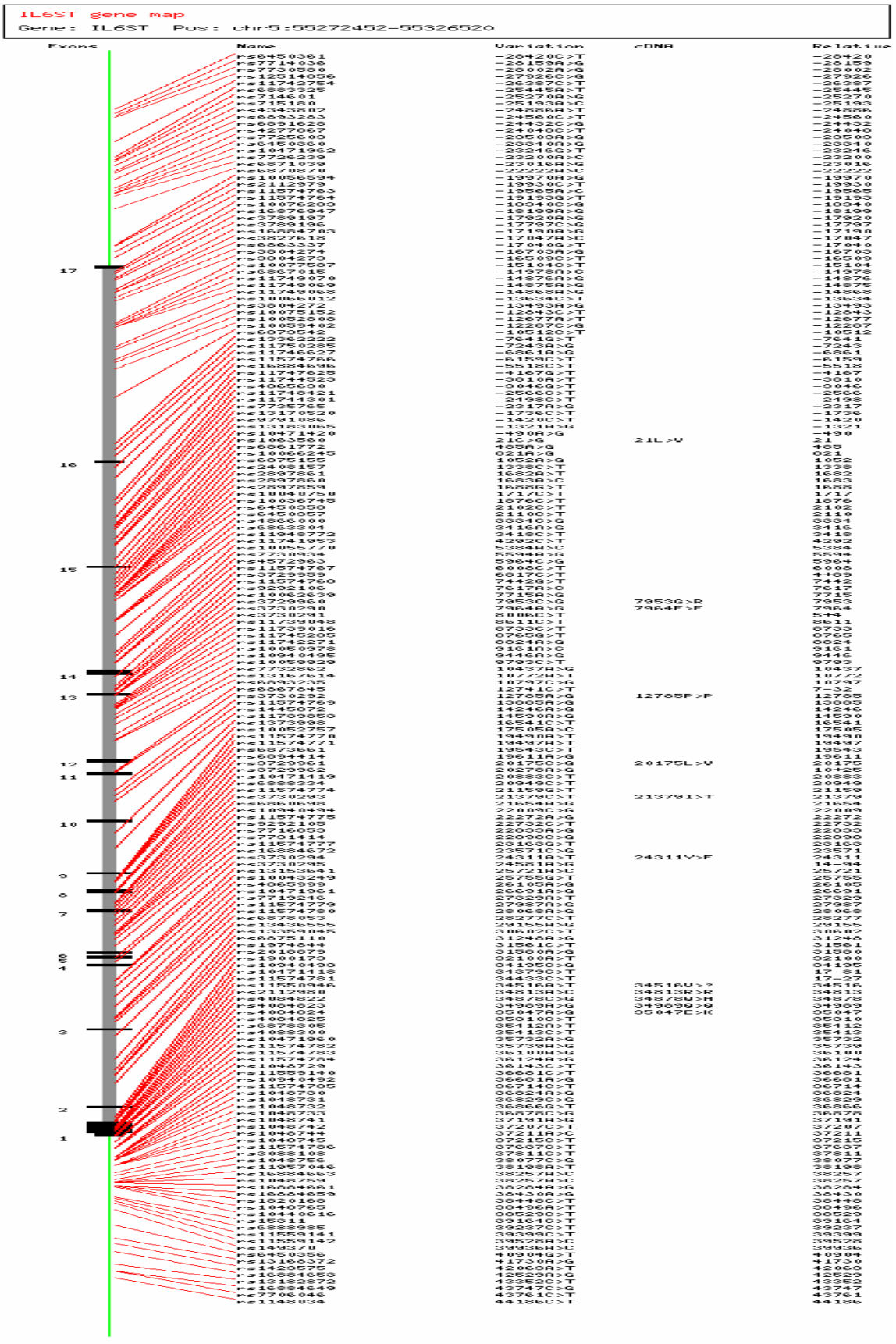
TP990780GS	case	**CG**	**AG**		TP992800PW	control	**CC**	**AA**
TP990782CK	control	**CC**	**AA**		TP992804SJ	control	**GG**	**GG**
TP990783SM	control	**CG**	**AG**		TP992808CA	case	**CG**	**AG**
TP990785KS	control	**CG**	**AG**		TP992822VR	case		**AA**
TP990786AJ	control	**CG**	**AG**		TP992824HG	case	**CG**	**AG**
TP990787FM	control	**CG**	**AG**		TP992825JW	case		**AA**
TP990789DL	case	**CG**	**AG**		TP992832EB	case		
TP990791AA	control	**CG**	**AA**		TP992852AS	control	**CC**	**AG**
TP990792AR	case	**CG**	**AG**		TP992855GB	case		**AA**
TP990793RL	case	**CC**	**AA**		TP992861ET	control	**CG**	**AG**
TP990796LG	case	**CG**	**AG**		TP992864HT	case		**AA**
TP990797UA	case	**GG**	**AG**		TP992866JR	control	**CG**	**AA**
TP990798FO	control	**GG**			TP992868IW	control	**GG**	**GG**
TP990801HR	case	**CG**	**AA**		TP992870RK	case	**CG**	**AG**
TP990803GM	control	**CG**	**AG**		TP992871WL	control	**GG**	**GG**
TP990805GB	control	**GG**	**AG**		TP992874LA	control	**GG**	**GG**
TP990808WG	control	**CG**	**AA**		TP992877JE	control	**CC**	**AG**
TP990810GL	case	**CG**	**AG**		TP992880CL	case	**CG**	**AG**
TP990816KC	control	**CG**	**AG**		TP992882ES	case	**GG**	
TP990819TN	control	**GG**	**AG**		TP992885MM	control	**GG**	
TP990826MC	case	**CG**	**AA**		TP992886KT	control	**CG**	**AG**
TP990827RC	control	**CC**			TP992894RS	control	**CC**	**AA**
TP990828NC	control	**CC**	**AA**		TP992898HA	control	**GG**	**GG**
TP990830NN	control	**CG**	**AA**		TP992899SG	control	**CC**	**AA**
TP990835WM	control	**CC**	**AA**		TP992904HM	control	**CC**	**AA**
TP990837CL	case	**GG**	**AG**		TP992906LM	control		**AG**
TP990841WW	control	**CG**	**AA**		TP992911AG	case		**AG**
TP990844LT	control	**CG**	**AA**		TP992913CE	control	**CG**	**AG**
TP990845IM	control	**CG**	**AG**		TP992914AJ	control	**GG**	**GG**
TP990848FM	control	**GG**			TP992923HD	control	**CG**	**AA**
TP990851WP	control	**CG**	**AG**		TP992925AH	control		
TP990853IS	control	**CG**	**AG**		TP992927GJ	control	**CC**	**AA**
TP990854TW	control	**CC**	**AA**		TP992934OM	control	**GG**	**AG**
TP990855RC	control	**CC**	**AA**		TP992936PB	case	**CG**	**AG**
TP990856ES	control	**CG**	**AG**		TP992938JQ	control	**CG**	**AG**
TP990857EJ	case	**GG**			TP992941BA	control	**CC**	**AA**
TP990858MN	control	**GG**	**GG**		TP992944MJ	control	**CG**	**AG**
TP990861LM	control	**CG**	**AG**		TP992946RC	control		**AG**
TP990862JB	case	**CC**	**AA**		TP992950CA	control	**CG**	**AG**
TP990864AF	case	**CC**	**AA**		TP992951PC	control	**CG**	
TP990869AC	control	**CC**	**AA**		TP992953VW	control	**GG**	
TP990871CJ	case	**GG**			TP992954SS	control	**CG**	**AA**
TP990879LM	case	**CC**	**AA**		TP992955IM	control	**CG**	**AG**
TP990883EM	case	**CC**	**AA**		TP992957CO	control	**CC**	**AA**

TP990885AN	case	**CG**	**AG**		TP992961PI	control	**CG**	**AG**
TP990889AN	control	**CG**	**AG**		TP992964DW	control		
TP990898SB	control	**CG**	**AG**		TP992965RB	control	**CC**	**AA**
TP990900JJ	control	**CG**	**AG**		TP992967AS	case	**CC**	**AA**
TP990902HR	case		**AA**		TP992972ES	case	**CG**	
TP990903CM	case	**CG**	**AG**		TP992975HG	case	**CG**	**AG**
TP990907HB	control	**CG**	**AG**		TP992976CE	case	**CG**	**AG**
TP990908VT	control	**CC**	**AA**		TP992977HK	control	**CG**	**AA**
TP990911EB	control	**CG**	**AA**		TP992981HM	control	**CG**	**AG**
TP990912HJ	case	**GG**	**AG**		TP992987LD	case	**GG**	**GG**
TP990920JJ	control	**CC**	**AA**		TP992988DA	control	**CG**	**AG**
TP990923CN	control	**CG**	**AA**		TP992989WB	control	**CG**	**AG**
TP990924ET	control	**CG**	**AG**		TP992992BK	control	**CG**	**AG**
TP990929GD	case	**CG**	**AA**		TP992996FA	control	**GG**	**AG**
TP990933SD	case		**AG**		TP993000LB	case	**GG**	**GG**
TP990934EJ	control	**CG**	**AG**		TP993003RW	control	**CC**	
TP990936AT	control	**GG**	**AG**		TP993005JP	case	**CG**	**AG**
TP990937PD	control	**CG**	**AA**		TP993019BM	case	**CG**	
TP990938GB	control	**CG**			TP993022RP	control	**CC**	
TP990940CC	control	**CG**	**AG**		TP993052AA	case	**CC**	**AA**
TP990941GS	control	**CG**	**AG**		TP993071TD	case	**CG**	
TP990944CA	control	**GG**	**GG**		TP993097RB	case	**CG**	
TP990946AT	case	**CG**	**AG**		TP993100NN	case	**CG**	**AG**
TP990952LG	control	**CC**	**AA**		TP993101FP	case	**CG**	**AG**
TP990954CW	control		**GG**		TP993118WJ	case	**CC**	**AA**
TP990956CA	control	**CG**	**AG**		TP993142GG	control	**CG**	**AG**
TP990957WP	control	**GG**	**AA**		TP993149ND	control	**CG**	
TP990959RC	control	**CC**	**AA**		TP993150RV	control	**GG**	**AG**
TP990967AC	control	**CG**	**AA**		TP993151SJ	control	**CG**	**AG**
TP990971SJ	case	**CC**	**AA**		TP993152DC	case	**CC**	
TP990976FC	control	**GG**	**GG**		TP993154RC	control	**CG**	**AG**
TP990991CO	control	**CG**	**AA**		TP993159WT	control	**CC**	**AA**
TP991008RF	control	**CG**	**AA**		TP993160HT	control	**CC**	
TP991011DS	control	**CG**	**AA**		TP993163CR	control	**CG**	**AG**
TP991012CJ	case	**GG**	**GG**		TP993164VR	control	**CG**	**AG**
TP991014CM	case	**CG**	**AG**		TP993165ED	case	**GG**	
TP991015CW	case	**CG**	**AG**		TP993171ES	control	**GG**	
TP991016CM	control	**CC**	**AA**		TP993175FB	control	**CC**	
TP991020VT	case	**CC**	**AA**		TP993178AM	control	**CC**	
TP991025CC	control	**GG**	**GG**		TP993184MA	control	**CC**	
TP991027IW	control	**CG**	**AG**		TP993185CR	control	**GG**	
TP991033CS	case	**CG**	**AA**		TP993186CC	control		
TP991038TN	control	**CC**	**AA**		TP993187WW	case	**CG**	**AG**
TP991039GO	control	**CG**	**AG**		TP993188SG	control	**GG**	

TP991041HC	control	**CG**	**AG**		TP993191ET	control	**CC**	**AA**
TP991043JI	control	**CG**	**AG**		TP993194NR	case	**CG**	**AA**
TP991044CR	control				TP993196SH	case	**GG**	**GG**
TP991047KP	control	**CG**	**AG**		TP993197MM	control	**CC**	**AG**
TP991048CG	control	**GG**	**GG**		TP993198RR	control	**CC**	**AG**
TP991054DS	control	**CC**	**AA**		TP993202EC	case	**CG**	**AA**
TP991056NJ	control	**CG**	**AG**		TP993203BB	control	**CG**	**AG**
TP991057CS	control	**GG**	**GG**		TP993205CR	control	**CC**	**AA**
TP991058WC	case	**CG**	**AA**		TP993206JB	case	**CG**	
TP991059RA	case	**GG**	**AG**		TP993239LC	case	**CG**	**AA**
TP991060ED	control	**GG**	**GG**		TP993246MN	case	**CG**	**AG**
TP991061AS	control	**CG**	**AG**		TP993262MP	control	**CC**	
TP991063AD	control	**CG**	**AA**		TP993269DR	control	**GG**	**AA**
TP991065VM	control	**CC**	**AA**		TP993273AA	control	**CG**	**GG**
TP991069ME	control	**CC**	**AA**		TP993285KD	control	**CC**	**AG**
TP991070LG	control	**CG**	**AA**		TP993299NC	case	**GG**	**AA**
TP991074SG	control	**CG**	**AA**		TP993308MG	case	**CG**	**AG**
TP991075CG	control				TP993314EP	control	**GG**	**AA**
TP991077MW	case	**CG**	**AG**		TP993316CC	case	**CG**	**AA**
TP991080AH	control	**CC**	**AA**		TP993319EB	control	**CG**	**AA**
TP991081VJ	control	**CG**	**AG**		TP993325OC	control	**CG**	
TP991084OM	control	**CG**	**AG**		TP993326WH	control	**CG**	**AA**
TP991090VL	case	**CC**	**AA**		TP993330RR	case	**CG**	**AA**
TP991093SJ	case	**GG**	**AG**		TP993331GB	control	**GG**	**AA**
TP991097FW	control	**CC**	**AA**		TP993333RR	control	**CC**	**AG**
TP991098FB	control		**AG**		TP993334DP	control	**CC**	**AG**
TP991099KJ	control	**GG**	**GG**		TP993336HS	control	**CC**	**AA**
TP991103KC	control	**CC**	**AA**		TP993339EB	control		
TP991105PY	control	**GG**	**AA**		TP993358RH	case	**CC**	**AG**
TP991107CD	control	**CG**	**AA**		TP993359EW	control	**CC**	**AG**
TP991114CC	control	**CG**	**AG**		TP993367RR	control	**GG**	**GG**
TP991116NM	control	**CC**	**AA**		TP993368LW	case	**CC**	**AG**

Appendix B

GENE MAP OF IL-6ST


IL6ST gene map
Gene: IL6ST Pos: chr5:55272452-55326520
Exons
Name
Variation
cDNA
Relative

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