TRANSCRIPTOME ANALYSIS OF T CELLS IN CHROMOSOME 22Q11.2 DELETION SYNDROME

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Date Defended: 19 November 2018

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Date Approved: December 4, 2018

Abstract

Background

Phenotypic variations of chromosome 22q11.2 deletion syndrome (22qDS) have no clear explanation. T cell lymphopenia in chromosome 22q11.2 deletion syndrome (22qDS) is related to varying degrees of thymic hypoplasia and contributes to the phenotypic heterogeneity. No phenotype correlation with genotype or deletion size is known for lymphopenia. We hypothesized that the T-cell transcriptome is different in 22qDS compared to healthy children and that gene expression in T cells can differentiate patients with low T cells compared to normal T cells.

Methods

Peripheral blood was collected from a convenience sample of participants aged 5-8 years. Standard immune function testing was performed. RNA sequencing was completed on isolated T cells using Illumina's TruSeq technology. Differential gene expression profiles ($q<0.05$) of T cells between 22qDS and healthy controls were determined with Tuxedo Suite & String Tie pipelines. Bioinformatic analyses were implemented via Ingenuity Pathway Analysis and KEGG to identify enriched pathways. The Spearman correlation between gene expression and clinical variables were calculated using SAS (9.4, Cary, NC) (p-value<0.05).

Results

A total of 360 genes were differentially expressed between T cells of 22qDS patients (n=13) and healthy controls (n=6) (Log 2 fold change range (-2.0747, 15.6724)).When these 360 genes were tested for pathway enrichment, the top 5 pathways in T lymphocytes based on their p value included communication between innate and adaptive immune cells, cross talk between dendritic cells and natural killer cells, allograft rejection signaling, dendritic cell maturation, and B cell receptor signaling. The top 10 biological processes with differential expression included 36 immune response, 31 inflammatory response, 33 apoptotic process, 12 interferon gamma mediated signaling pathway, 14 nucleosome assembly, 16 defense response to virus, 8 lipopolysaccharide mediated signaling pathway, 7 positive regulation of NF-kappa B import into nucleus, 10 type I interferon signaling pathway, and 10 neutrophil chemotaxis genes. We compared gene expression between 22qDS participants with low T cell counts (n=7) and 22qDS participants with normal T cell counts (n=6) and found 94 genes that were differentially expressed ($q<0.05$) (Log2 fold change range (-4.5445, 5.1297)). We found 29 genes that correlated with T cell counts and subsets (CD3, CD4, CD8, and naïve helper T cells) ($R\geq0.8$).

Conclusions

T-cell gene expression contributes to phenotypic heterogeneity in chromosome 22q11.2 deletion syndrome. T cell gene expression is different in 22qDS with low T cells compared to normal T cells. Differential gene expression can be used in future to develop biomarkers to differentiate between different phenotypes of 22qDS. Further, therapies can be personalized based on the phenotype using RNA therapeutics.

Acknowledgments

I would like to thank my mentors Marcia A. Chan, PhD and Daniel P. Heruth, PhD, late Shui Qing Ye, PhD for their guidance, support, and helpful tips to help me succeed. I would like to thank my thesis committee for their time and input. I appreciate all the work that Janelle R. Noel-Macdonnell, PhD put in my thesis and would like to thank her for her contribution. I would like to thank my research coordinators and laboratory research staff for all their work. I could not have done this study without the funding support for New Investigator Award from Children's Mercy. The contribution of the patients and families is invaluable. I would like to thank SuperQ team and Allergy/ Asthma/ Immunology team at Children's Mercy Hospital for their support through this process. Last but not the least, I would like to thank my husband Sanket Shah, my daughter Shriya Shah, my parents, rest of my extended family, and friends for their support and encouraging words throughout my academic journey so far.

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Chapter 1: Introduction

Chromosome 22q11.2 deletion syndrome (22qDS), a disorder with heterogeneous phenotype, is the most common micro deletion chromosomal disorder, affecting at least one in 4000 live births every year [1, 2]. Based on this incidence, the minimum estimate of burden of the disease in the United States is 81,430 for the 2017 US population. Infant mortality of 8% and premature adult mortality (median survival of 41.5 years) of 11% is attributable to 22qDS [3, 4]. The average health care cost of a patient with 22qDS from prenatal care to age 20 is $727,178 with the cost being significantly higher for patients with low T cell counts [5]. Overall, the varied phenotype involving various systems is responsible for the morbidity and mortality associated with 22qDS. Understanding the molecular mechanisms underlying the phenotypic heterogeneity could lead to development of personalized treatments and improved outcomes.

The remarkable clinical heterogeneity noted in 22qDS is due to diverse combinations of anomalies in various organ systems that differ in presence and severity [4-6]. Historically, patients were thought to have distinct disorders named as DiGeorge syndrome, velocardiofacial syndrome (VCFS), Opitz/GBBB syndrome, Shprintzen syndrome, conotruncal anomalies face syndrome, CATCH 22, Cayler syndrome, and Sedlockova syndrome and were eventually found to have chromosome 22q11.2 deletions. [7-10].

Clinical features are a result of combinations of cardiac anomalies, hypoparathyroidism, gastrointestinal, developmental, behavioral, neurological, skeletal, renal, dental, ophthalmological, velopharyngeal insufficiency, and immunological involvement [4, 6]. The most common cardiac anomalies noted in various cohorts are Tetralogy of Fallot, Tetralogy of Fallot with pulmonary valve atresia, ventricular septal defect, interrupted aortic arch, and truncus arteriosus [11]. Hypoparathyroidism can lead to hypocalcemia and is noted in 30-60% patients

with 22qDS in various cohorts [4, 12-14]. Palatal anomaly has been noted in 69% of patients with 22qDS [6]. These anomalies include cleft palate, submucosal cleft palate, bifid uvula, and velopharyngeal insufficiency. 22qDS affects growth in most patients with 36% below 3rd percentile which can be associated with growth hormone deficiency in some patients [4, 15]. Developmental delays including speech, gross motor, fine motor, and intellectual are common in patients with 22qDS [16, 17]. Hearing loss has been noted in 33% patients with 22qDS [4, 18]. Behavioral issues include anxiety, depression, autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and schizophrenia [19, 20] . Skeletal anomalies such as cervical spine anomaly, butterfly vertebrae, club foot, polydactyly, syndactyly, and scoliosis (0.6-60%) have been reported in patients with 22qDS [21, 22]. Renal anomalies such as unilateral renal agenesis, bilateral duplex kidneys, multicystic dysplastic kidneys, small kidneys, vesicoureteral reflux, and nehrocalcinosis have been reported in 36-38% patients with 22qDS [4, 23, 24]. Gastrointestinal issues described in 22qDS include feeding and swallowing issues, esophageal dysmotility, intestinal malrotation, nonrotation, Hirshsprung disease, tracheoesophageal fistula, constipation, and gastroesophageal reflux [18, 25]. Numerous neurological, ophthalmic, dental anomalies or issues have been reported in 22qDS [4, 18, 26, 27]. About 77% of patients with 22qDS have immune dysfunction [28].

The immunodeficiency in 22qDS has a wide spectrum. The most severe presentation is associated with complete absence of T cells due to defective T cell development secondary to thymic aplasia [4, 29]. Treatment for these patients requires adoptive T lymphocyte transfer or thymic transplantation for survival [30, 31]. Besides the severe immunodeficiency, thymic hypoplasia can result in T cell lymphopenia of varying degrees that can change with age [32, 33]. Other immunological abnormalities include impaired T cell function, restricted T cell receptor

repertoire, and impaired humoral or B cell function [34-36]. Immunodeficiency in 22qDS frequently leads to recurrent, life-threatening infections and autoimmune manifestations [3, 37, 38]. About 25-27% patients with 22qDS have recurrent sinusitis or otitis media, while 4-7% have recurrent lower respiratory infections in a study of 55 patients [35]. About 0.5% to 1% of patients have severe combined immunodeficiency which is fatal unless identified early and treated with hematopoietic stem cell transplant [4, 39]. Autoimmune manifestations occur in 8.5-10% of 22qDS patients [39].

Various theories have been tested to investigate this phenotypic variability. Ninety percent of 22qDS patients have a 3Mb deletion (typical deleted region; TDR) involving low copy repeat (LCR) regions A to D, while 10% have atypical deletions (~1.5 or rarely 2 Mb) [40]. Size of the deletion has failed to show a correlation with phenotypes [40]. Resolution of the breakpoints for the deletion in the LCR regions showed the TDR was at least 2,381,238 base pairs (bp) long. The extent of the deletion has not been linked with phenotypic variation [41]. Recently, a study showed that T cells counts in 22qDS were significantly lower with chromosomal deletion in T-box transcription factor (*TBX1*) region (LCR A-B, A-C, A-D) compared to the ones excluding *TBX1* region (LCR B-D, C-D, D-E, D-F) [42]. Despite the identical chromosomal deletion, there is an impressive diversity in the phenotypes including immune phenotypes noted in 22qDS. Numerous copy number variants (CNVs) are found in the rest of the genome of 22qDS and may contribute to the variation in phenotype, but a particular CNV has not been associated with a specific phenotype [43]. Earlier studies found a correlation of variations in a few genes such as synaptosomal-associated protein 29 (*SNAP29*), catechol-O-methyltransferase, and *TBX1* with phenotypic variation [44-48]. While some studies show *TBX1* to be associated with cardiovascular anomalies, a study looking at 1,022 subjects did not find a correlation of variants in *TBX1* gene

with cardiovascular anomalies in 22qDS [47-50]. While these phenotypic correlations provide valuable insight, other studies show that genotype-phenotype correlations have failed to adequately explain the clinico-pathological mechanism underlying diverse manifestations of 22qDS [51]. Besides, the type and severity of the features can vary in individuals from the same family that carry the deletion suggesting possible role of gene expression affecting the spectrum of clinical features [52].

Since there is a lack of phenotypic correlation with genotype, CNVs, breakpoints, or deletion size we hypothesized that the phenotypic heterogeneity in 22qDS can be explained by differential gene expression. Limited number of studies have used RNA microarrays to study noncoding RNA such as microRNA (miRNA) and long noncoding RNA (lncRNA) [41, 53]. RNA sequencing has been done in neuronal cells in 22qDS to study occurrence of schizophrenia in 22qDS [54]. Our aim was to study the transcriptome of peripheral T lymphocytes in 22qDS using RNA sequencing (RNA-seq) to explain the phenotypic heterogeneity in 22qDS.

Chapter 2: Methods

Study Methods

We performed a single-centered study involving a convenience sample of participants along with retrospective chart review. This study was approved by Children's Mercy Hospital (CMH) Institutional Review Board. Participants included patients referred to a multidisciplinary clinic at CMH for management of chromosome 22q11.2 deletion syndrome. Healthy control participants were recruited by recruitment announcements in the hospital. Written informed consent was obtained from parents/ legal guardians of all the participants.

Subjects and Samples

We recruited patients with 22qDS and healthy controls from children aged 5-8 years as other studies have shown that gene expression can change with chronological age in various cells including T cells [55-57]. While these studies looked at age-related transcriptional changes in adults, we decided to study a narrow pediatric age group with the aim to reduce age related differential expression of genes. Inclusion criteria for patients in the study included patients with chromosome 22q11.2 deletion confirmed by FISH or microarray who were aged 5-8 years. Exclusion criteria were used to minimize the differential gene expression related to acute or other unrelated chronic conditions. These included: participants on corticosteroid therapy in preceding 2 weeks, on biological or chemotherapeutic drugs, patients with chronic kidney or liver disease or cancer, or those deemed by the investigator to have altered immune system from other causes. In order to ensure that milder phenotypes of undiagnosed 22qDS were not included as controls we ruled out 22qDS clinically in healthy controls by confirming absence of cardiac defects, hypocalcemia, recurrent infections, typical facial features, developmental/ psychiatric issues, and velopharyngeal defects.

Sample Preparation and Processing

Peripheral blood processing. Peripheral blood was collected, and mononuclear cells were isolated by density gradient centrifugation. T cells (CD3+) were isolated using a negative selection EasySep magnetic beads kit (STEMCELL Technologies, Vancouver, BC).

RNA isolation. RNA was extracted using the Ambion mirVana™ RNA extraction kit following the manufacturer's protocol. RNA was quantified with an Epoch 2 spectrophotometer (BioTek, Winooski, VT). The RNA integrity of each sample was assessed using an Experion™ automated electrophoresis station (Bio-Rad, Hercules, CA). Aliquots of RNA from each sample were used for RNA sequencing and cDNA synthesis. The remaining RNA was stored at -80ºC.

RNA sequencing. RNA-seq was performed in the CMH Core of Genetics Research Laboratory. Each RNA sample (1 µg) was converted into libraries of cDNA and prepared for sequencing using the Illumina TruSeq RNA sample preparation kit. Clusters of identical sequences were generated using an automated amplification system (Illumina cBot). High output RNA-seq was performed by paired-end (2×101) deep sequencing coverage (104X) using Illumina's TruSeq technology on the Illumina HiSeq1500. The resulting base calling (.bcl) files were converted to FASTQ files using Illumina's bcl2fastq v2.17.1.14 software. The Tuxedo Suite pipeline (TopHat v1.3.0/Bowtie v0.12.7/Cufflinks v1.0.3) was used to map RNA-seq reads and to determine transcript assembly and abundance estimations in Fragments Per Kilo base of exon per Million fragments mapped (FPKM) following the published procedures [58-60]. Cufflinks calculates false discovery rate (FDR) (q-value) via Benjamini-Hochberg correction. Fold-change (FC) was calculated by dividing either the FPKM for individual cases (22qDS) or the mean FPKM for all cases by the mean FPKM for controls. Fold-change was log (log2) transformed for normal distribution.

Clinical data and immunological assays. Basic immunological evaluation was performed for all participants from the same blood specimen used for RNA sequencing. Complete blood counts and differential counts, lymphocyte subsets by flow cytometry (T cells or CD3+, T helper subset or CD3+CD4+, T suppressor/cytotoxic or CD3+CD8+, B cells or CD19+, NK cells or CD16/56+), along with naïve and memory T cell subsets, immunoglobulin G, A, M levels, were tested at the Hematology, Flow cytometry, and Immunology laboratories at Children's Mercy Hospital. Specimens to be tested for vaccine titers (Pneumococcal titers-23 serotypes and Tetanus titers) were sent from the CMH laboratory to the Mayo Immunology laboratory for processing. The rest of the laboratory data such as lymphocyte proliferation to mitogen/ antigen stimulation and calcium levels along with other clinical data were obtained by retrospective chart review using REDCap database [61]. Laboratory data including lymphocyte count were considered low if the lab value/ count was less than 2 standard deviation (SD) compared to normal for age appropriate laboratory reference range. Pneumococcal titers were considered low if the titer was <1.3. If a participant had <50% protective titers for a 5-year-old or <70% for 6 and older, titers were considered low. Tetanus titers were considered low if the level was <0.15. Patients with 22qDS were grouped as having low and normal T cell counts based on CD3 count lower than 2SD compared to normal laboratory reference range. These two groups of patients were compared to healthy controls.

Real time polymerase chain reaction validation assays. Differentially expressed gene candidates were validated using the comparative CT method. Complementary DNA (cDNA) was generated by reverse transcription of 1 µg RNA primed with random hexamers using the Superscript™ IV First Strand Synthesis System (Thermo Fisher). Gene specific TaqMan™ Expression Assays were completed according to the manufacturer's guidelines using a TaqMan™

gene expression master mix (Thermo Fisher) and the eukaryotic 18S rRNA endogenous control (Thermo Fisher) on a ViiATM 7 Real Time PCR System (Thermo Fisher). The ΔΔCT was calculated by subtracting the mean ΔCT for the normal control group from the mean ΔCT for each 22qDS sample.

Statistical analysis

Annotation. Cuffdiff uses the test statistics T=E [log(y)]/Var [log(y)], where y is the ratio of the normalized counts between two conditions, and this ratio approximately follows a normal distribution [62]. Hence a t-test is used to calculate the p-value for differential expression. We employed multiple test correction and used q value to determine statistical significance via Benjamini-Hochberg correction. Genes with a significant expression change between 22qDS participants and healthy controls and later on between 22qDS with normal T cells and those with low T cells ($q<0.05$) were submitted for Ingenuity Pathway Analysis (www.ingenuity.com) to gain insight into the biological relationships and signal transduction cascades altered in 22qDS patients. In order to identify networks pathways that are enriched by the differential gene expressions between 22qDS and healthy controls, we used the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database [63-65]. We also used Gene Ontology (GO) database to gain insight on the affected biological processes based on the differential gene expressions between 22qDS and healthy control participants [66, 67].

Statistical analysis for clinical variables. Clinical and laboratory variables were descriptively summarized for all study participants and further summarized by their disease group. Means and standard deviations are reported for continuous variables. Categorical variables are described using frequencies and percentages. Differences between the study groups were assessed using two-sided independent t-tests (for continuous variables) or Chi-Square or Fisher's exact tests (for categorical

variables) as appropriate based on cell counts. We used Spearman's correlation to evaluate for a correlation between gene expression and clinical/laboratory variables. A p-value of <0.05 was used to define significance.

Chapter 3: Results

Subjects

We enrolled a total of 20 participants. We performed RNA sequencing on peripheral T lymphocytes in 13 participants with 22qDS and 6 healthy control participants. We excluded one participant due to extremely low specimen volume that did not yield T cells. Patients with 22qDS were further divided into two groups, patients with had low T cell counts (n=7) and patients with normal T cell counts (n=6) based on CD3+ counts. The mean participant age was 6.91 (± 1.28). All patients were Caucasian except one (mixed race: Caucasian and Hispanic, participant identified as Hispanic) (Table 1).

Clinical data

By study definition, healthy controls did not have cardiac, developmental, behavioral issues, recurrent infections, calcium issues, or velopharyngeal anomalies. Clinical features among patients with 22qDS were common (See Table 2). One patient had hypocalcemia. Calcium level for patients with low T cells (9.48 ± 0.22) and normal T cells (9.28 ± 0.13) showed no significant difference (p =0.168). Growth hormone deficiency was noted in four patients (an additional patient was under evaluation and another did not qualify for testing due to global developmental delay). Neurological features included cerebral atrophy (1) and seizures (4). These were absence seizures or focal seizures. Among participants with 22qDS, 92.3% (12/13) had at least 1 developmental delay: 5 had gross motor delays, 5 had fine motor delays, 11 had speech delays, and 7 had identified intellectual delays. Twelve participants had difficulty with school performance, and 11 received at least some type of neurodevelopmental intervention. One patient had global developmental delay. Attention deficit hyperactivity disorder (ADHD) was noted in four patients, and anxiety was noted in two patients. Eight other patients had other behavioral issues including aggressive behavior,

disruptive behavior, screaming, tantrum, or inattentiveness / hyperactivity without diagnosis of ADHD. None of the patients had a diagnosis of schizophrenia. Cardiac defects (8 patients) among patients with 22qDS included atrial septal defect (ASD) (n=3), ventricular septal defect (VSD) (n=2), Tetralogy of Fallot (n=1), interrupted aortic arch (n=1), and other (n=7). Other cardiac findings included left aortic arch with aberrant right subclavian artery-benign variant, right aortic arch with or without aberrant subclavian with or without vascular ring, patent foramen ovale (PFO), patent ductus arteriosus (PDA), aberrant subclavian artery, absent pulmonary valve, and bicuspid aortic valve. Ten patients had recurrent infections that included pneumonia, otitis media, upper respiratory infections, sinusitis, bronchiolitis, skin and subcutaneous infections. Cleft palate (n=3), sub mucous cleft (n=1), velopharyngeal insufficiency (VPI) (n=6) types of palatal anomalies were reported in 9 22qDS patients. Hearing loss data were only available for four patients. Three patients had hearing impairment and two needed hearing aids. Hearing was not assessed in one patient due to global developmental delay. Five patients were noted to have feeding difficulties including three patients with gastrointestinal tube feeds. Three patients had GERD. Renal (n=5), ophthalmic (n=5), dental (n=7), and skeletal (n=8) anomalies were also noted in the 22qDS study patients.

Laboratory data

Table 3 summarizes the cell counts for all participants. Since the 22qDS groups were based on their CD3 counts, the corresponding mean white cell count ($p=0.022$), mean absolute lymphocyte count ($p<0.001$), and mean T cell subsets were noted to be different in the three groups. Platelet count was also lower in the 22qDS groups compared to healthy controls ($p=0.026$). Table 4 provides immunoglobulin (Ig) levels and vaccine titers in all participants. We found that mean IgG and IgA levels were significantly higher in normal and low T cell groups compared to

healthy controls (p=0.033 and p=0.028, respectively). However, the mean IgM level was significantly lower in low and normal T cell groups compared to healthy controls (p=0.013).

Quality analysis of RNA-seq data

RNA-seq data quality analysis for 19 participants showed a yield of 2,022 to 9,129 megabases. Clusters passing quality filter ranged from 10,007,826 to 45,192,971 (94.6% to 97.4% clusters). Q30 scores were in the range of 91.1 to 95.2%.

Gene expression

Of the 60,658 genes annotated (Genome Reference Consortium Human Build Homo_sapiens.GRCh38.83), 23,518 genes were expressed in participants. T cells of healthy controls expressed (non-zero count) 17,653 genes. A total of 21,597 genes were expressed in peripheral T cells of 22qDS patients.

We found 360 genes to be differentially expressed in peripheral T cells of 22qDS participants compared to those of healthy controls ($q<0.05$) (Supplemental Table 1). Among these, 250 genes were up regulated and 110 genes were down regulated in peripheral T cells of 22qDS participants compared to the healthy controls (Figure 1). Out of these 360 genes, 276 genes showed a 2-fold or greater change compared to controls.

There were 1,221 genes that showed differential expression by $p<0.05$. Out of these, 524 genes showed at least 2-fold change with 447 showing increase in expression while 77 showed at least two-fold decrease in expression in 22qDS compared to healthy controls. The aim of this analysis was not to show significance but to identify genes that could be of interest.

Among the genes in the typically deleted region on chromosome 22q (22:18906027:21396590), we found 15 genes to be differentially expressed in patients with 22qDS compared to healthy controls (Figure 2Figure 2). We checked the expression of genes that have

previously been associated with clinical features in 22qDS and did not see a significant difference in expression (all with q≥0.05*)*. These included *TBX1* (p-value =1, log2 FC = -1.83), *HIRA* (p value 0.0099, < 2 fold change), *COMT* (p-value 0.00795, log2 FC=-1.10), and *SNAP29* (p-value=0.0794, <2 FC).

Network and pathway analysis

The list of 360 differentially expressed genes was submitted to Ingenuity Pathway Analysis (IPA). Based on the algorithms applied, the top canonical pathways noted to be involved included communication between innate and adaptive immune cells, cross talk between dendritic cells and natural killer cells, allograft rejection signaling, dendritic cell maturation, B cell receptor signaling, and the other top pathways (Table 5). The top upstream regulators, diseases and disorders, molecular and cellular functions, as well as physiological systems are as noted in following tables (Table 6, Table 7, Table 8, Table 9 respectively). We identified the top upstream regulators with differential expression in our participants that were noted to be activated or inhibited (Table 6). The top diseases identified by IPA algorithm agree with the clinical picture of 22qDS that involves inflammation, immune defects, infections, and cancer (Table 7). The top cellular processes involve cell death, survival, growth, proliferation, development among others which suggest a possibility of T cell turnover affecting T cell counts in 22qDS (Table 8). There are 118 genes involved in lymphoid tissue structure and development and 103 genes involved in immune cell trafficking were among the 360 genes (Table 9).

In order to get further insight into the pathways enriched in T lymphocytes, we used KEGG pathway analysis as noted in (Table 10). The pathways that were enriched included systemic lupus erythematosus, graft versus host disease, type I diabetes mellitus, NF-kappa B signaling pathway, and allograft rejection. All these pathways show involvement of immune or autoimmune process.

We also used GO database to identify the top 10 biological process enrichments in the differentially expressed genes (Table 11). These genes included 36 immune response, 31 inflammatory response, 33 apoptotic process genes among numerous other immune mediated biological processes. The top 10 cellular components and molecular functions enriched in T lymphocytes compared to healthy controls are noted in Table 12 and Table 13 respectively. Both these algorithms identified MHC class II proteins affected that can play a role of innate immune cells in antigen presentation to T cells. This finding agrees with IPA and KEGG pathway analysis showing that communication between innate and adaptive immune cells is a major pathway that plays a role in 22qDS.

Analyses for immunological parameters

We also compared 360 genes in healthy controls to low and normal T cell count groups (Figure 3). Genes that were differentially expressed in 22qDS with low T cells compared to 22qDS with normal T cells were studied. We found 94 genes that were differentially expressed between these two groups ($q<0.05$) (Supplemental Table 2, Figure 4).

None of the 15 genes in typically deleted region that were differentially expressed in 22qDS compared to healthy controls showed differential expression when we compared 22qDS patients with low T cell counts to those with normal T cells (Figure 5). We sorted these 94 genes based on locus and found 7 genes on 22q locus (including the typically deleted region), *LGALS1 (upregulated), USP18 (downregulated), MYO18B (downregulated), FAM118A (downregulated), IGLV1-44 (upregulated), IGLV1-47 (upregulated),* and *IGLV2-8 (upregulated),* that were differentially expressed ($q<0.05$, two-fold change) between patients with low and normal T cell counts.

IPA analysis identified canonical pathways that were significant in 22qDS patients with low T cell group compared to normal T cell group (Table 14). LXR/RXR activation pathway, osteoarthritis pathway, communication between innate and adaptive immune cells, GADD45, and dendritic cell maturation were the top 5 enriched pathways.

We used CD3, CD4, CD8, and naïve T helper absolute counts for all 19 participants to find a correlation with gene expression. These cell counts were significantly correlated with 29 genes (Spearman correlation coefficient $R \geq 0.8$). (Supplemental Table 3)

Immunoglobulin G, A, and M levels did not show a significant correlation with expression of any genes (Spearman correlation coefficient $R < 0.8$).

Gene biotypes and noncoding genes

Out of 360 genes, 296 genes were protein coding genes. Biotypes of the noncoding genes are noted in Supplemental Table 4. These noncoding genes included 2 long intergenic noncoding RNA (lincRNA). *MIAT* is a lincRNA in 22q11.2 region that has previously been associated with myocardial infarction and schizophrenia ($q < 0.05$). *LINC00152/CYTOR,* another lincRNA, was found to be upregulated ($q < 0.05$, FC 1.1087) in 22qDS compared to healthy controls. *LINC00152* expression was negatively correlated to CD3 (R -0.71, $p < 0.001$), CD4 (R-0.73, $p < 0.001$), CD8 (R-0.61, $p = 0.006$), and naïve T helper cells (R-0.71, $p < 0.001$). This gene promotes cell proliferation.

RT-PCR Validation

We confirmed our findings by RT-PCR on 3 genes that were differentially expressed (Figure 5). Genes selected for validation included *DGCR2*, *MED15,* and *TRMT2A* that are located in the 22q critical region. Our PCR assays confirmed that the expression was decreased for the genes in the deleted region. Also, we validated our noncoding gene expression results. *MIAT* was decreased 1.5-fold in 22qDS patients compared to healthy controls.

Chapter 4: Discussion

Our study found 360 genes differentially expressed in the peripheral T cells of participants with chromosome 22q11.2 deletion syndrome compared to healthy controls. To our knowledge, ours is the first study describing RNA-seq results in T cells of patients with chromosome 22q11.2 deletion syndrome. Transcriptome studies in 22qDS so far have been done using RNA microarray on peripheral blood [53, 68]. Lin et al. described the transcriptome of induced pluripotent stem cell derived neurons in 22qDS using RNA sequencing [54]. T cell transcriptome has been studied by microarray and RNA sequencing in other disorders such as psoriasis, dermatomyositis and polymyositis [69, 70]. We focused on using RNA-seq to study T lymphocyte gene expression in 22qDS since T lymphocytes play a significant role in immunodeficiency associated with this disorder.

While none of the clinical features including recurrent infections were significantly different between the two groups ($p>0.05$), the phenotype variation that is typically noted with 22qDS was evident in our small group of patients.

Our study shows clear distinctions between T cell transcriptome of 22qDS patients and healthy controls regardless of their T cell counts. This brings up the question of whether T cells are responsible for the nonimmune phenotype of 22qDS. Both IPA diseases and GO biological process analyses show inflammatory response genes to be affected in 22qDS and may be playing a role in overall picture of 22qDS. While clinical immunodeficiency may not be evident in all 22qDS patients, the T cell gene expression is affected in all patients with 22qDS and sets them apart from healthy controls. Interestingly, one of our 22qDS patient had gene expression pattern similar to controls. We found that this patient had normal development compared to all other 22qDS patients who had at least some developmental delay.

Fifteen genes in the deleted region showed reduced expression in 22qDS compared to healthy controls. This finding suggests that despite the deletion, the remaining genes in the typically deleted region are either not expressed in T cells at all or are expressed similar to healthy controls. Several genes that have been previously shown to play a role in 22qDS phenotype were expressed similar to healthy controls such as *TBX1, HIRA, COMT, and SNAP29*. We think that these genes may not differentially expressed in T cells as compared to other tissues or peripheral blood.

Our study shows that the most significantly affected pathway in 22qDS is communication between innate and adaptive immune cells. Other involved pathways include cross talk between dendritic cells and natural killer cells, allograft rejection signaling, dendritic cell maturation, and B cell receptor signaling. The pathway most significantly affected by low T cells compared to normal T cells in 22qDS was LXR/RXR pathway. This pathway has been shown to be associated with regulation of T cell activation in mouse model [71]. Also, macrophage survival and innate immune response can be affected when LXR pathway has been affected [72-74]. These findings indicate that innate immunity plays a significant role in 22qDS phenotype.

Chromosome 22q11.2 deletion affects development of the thymus, the primary immune organ. Normally, developing T lymphocytes from bone marrow follow immune trafficking signals and get carried to the thymus for further maturation. IPA analyses identified genes involved in development of lymphoid tissue and immune cell trafficking to be differentially expressed in 22qDS compared to healthy controls. These genes showed positive activation scores suggestive of activated pathways and upregulation. These genes can provide further clues to the genes associated with thymic hypoplasia in 22qDS. Further analyses of enriched pathways, networks, and molecules

in 22qDS can ultimately lead to identification of therapeutic targets to develop personalized medicine for various phenotypes of 22qDS.

Our study identified 94 genes ($q<0.05$) that were differentially expressed in 22qDS with low T cells compared to 22qDS with normal T cells. We were particularly interested in looking at genes on 22q locus that might have an association with T cell counts. We found 7 genes that were differentially expressed (*LGALS1, USP18, MYO18B, FAM118A, IGLV1-44, IGLV1-47,* and *IGLV2-8).* Among the 7 genes located on 22q (outside the critical region), *LGALS1* was noted to show milder but significant correlation of *LGALS1* with CD3 ($R=-0.68$, $p=0.001$). *LGALS1* is normally expressed in the thymus, codes for galectin 1 protein, and has been shown to trigger T cell apoptosis [75]. Next, we used Spearman's correlation to identify 29 genes that showed high correlation with CD3, CD4, CD8, or naïve T helper cell counts. Comparing the 94 gene list and 29 gene list, we found 5 genes that were common to both lists including *GZMK, DUSP4, DUSP5, CDKN1A,* and *S100A8*. These genes are involved in cell cycle progression, cellular proliferation and differentiation, or cell lysis/ apoptosis. Further studies will be needed to investigate the association of these genes in low T cell counts noted with 22qDS. Such associations of gene expression with low T cells or other phenotypes of 22qDS can lead to development of biomarkers that identify such phenotypes. Future studies can use these findings to develop innovative therapies to provide personalized care to 22qDS with each phenotype and lead to improved outcomes.

Differential expression of miRNA has previously shown to play a role in phenotypic variation in 22qDS [53]. LncRNA have been shown to interact with miRNA and play a regulatory role in affecting gene expression [76]. We therefore looked at gene biotypes to identify lncRNA that may be differentially expressed in our patients with 22qDS. Our study showed that *LINC00152* was overexpressed in patients with 22qDS compared to healthy controls and was negatively

correlated to T cell counts and T cell subsets (CD3, CD4, CD8, and naïve T helper cells). *LINC00152* has been shown to affect cell proliferation. While previous studies have shown *LINC00152* to promote cell growth in various cancers, our study showed inverse correlation with cell counts [77-79]. One possibility is that the low cell counts may lead to increased expression of genes that can help with cell growth and proliferation. Or the role of *LINC00152* is different in T cells from that noted in other cells noted in cancers such as gastric cancer, oral squamous cell cancer, glioblastoma, and ovarian cancer. Further studies are needed to investigate the role of noncoding RNA in 22qDS.

We acknowledge the limitations of our study. Our study was conducted in children aged 5-8 years; therefore, these results may not be true for other age groups since gene expression can change with age especially in older age group. Further studies would be needed to investigate similar effects in other age groups. Though ideally, we would have liked to perform RNA sequencing on a single subset of T cells (such as naïve T helper cells), we chose to start with all CD3 positive T cells since T cell lymphopenia in some of the patients can be limiting in terms of feasibility of this project with one particular subset. While the rate of false positive results can be high with sequencing results given the multiple tests performed, we used multiple test correction and used q value to determine significance. Also, we recognize that it is possible that the change in CD4 and CD8 T cell subset counts may account for the differential gene expression rather than the total T cell/CD3 counts and can be studied as a next step. Finally, in our initial study we analyzed differential gene expression. The next step in this project will determine the effect of 22qDS on RNA processing resulting in the expression of alternative gene transcripts (isoforms).

Chapter 5: Conclusion

When considering the transcriptome of T cells in 22qDS, gene expression is significantly different in T cells of 22qDS and healthy controls. Also, gene expression for several genes shows correlation with low T cells and T cell subsets. Important pathways that are enriched by gene expression are communication between innate and adaptive immune cells, crosstalk between dendritic cells and natural killer cells, allograft rejection signaling, dendritic cell maturation, and B cell receptor signaling suggesting a role of innate immunity in this disorder. Further studies are needed to confirm and study the role of various differentially expressed genes and pathways in determining the phenotype of 22qDS. We hope that our study will lay a strong foundation to use T cell transcriptome in order to identify biomarkers that differentiate between various phenotypes of 22qDS. Thereby, differentially expressed genes can be used to develop therapies to personalize treatment for 22qDS with varied phenotypes.

Chapter 6: Tables and Figures

Tables:

Table 1*:*

Demographics

Demographic Feature	Group 22qDS with low T cells n = 7	22qDs with normal T cells n = 6	Healthy control n = 6	p-value
Sex				0.507
Female	2 (28.6%)	4 (66.7%)	2 (33.3%)	
Male	5 (71.4%)	2 (33.3%)	4 (66.7%)	
Race				1.000
Caucasian	6 (85.7%)	5 (83.3%)	6 (100.0%)	
Other	0 (0.0%)	1 (16.7%)	0 (0.0%)	
Missing	1 (14.3%)			
Ethnicity				0.826
Hispanic	3 (42.9%)	2 (33.3%)	1 (16.7%)	
Non-Hispanic	4 (57.1%)	4 (66.7%)	5 (83.3%)	

Table 2*:*

Clinical Features of patients with 22qDS with low T cells versus normal T cells

Characteristic	22qDS with low T cells N (%)	22qDS with normal T cells N (%)	p-value
Recurrent Infections	5 (71.4)	5 (83.3)	1.000
Cardiac defect	5 (71.4)	3 (50.0)	1.000
Hypocalcemia	1 (14.3)	0 (0.0)	1.000
Velopharyngeal defect	5 (71.4)	4 (66.7)	1.000
Growth hormone deficiency	3 (42.9)	1 (16.7)	0.790
Developmental delay	7 (100.0)	5 (83.3)	0.462
Behavioral/ psychiatric issue	6 (85.7)	4 (66.6)	0.416
Hearing loss[1]	2 (28.6)	1 (16.7)	1.000
Renal anomalies	3 (42.9)	2 (33.3)	1.000
Skeletal anomalies	5 (71.4)	3 (50.0)	0.592
Dental anomalies	3 (42.9)	4 (66.7)	0.592
Ophthalmological anomalies	2 (28.6)	3 (50.0)	0.138
Seizure	3 (42.9)	1 (16.7)	0.559
G-tube	3 (42.9)	0 (0.0)	0.192

[1] Hearing loss data was available for four patients.

Table 3:
Laboratory Data: Cell counts

Characteristic Mean (SD)	22qDS with low T cell counts	22qDS with normal T cell counts	Healthy controls	p-value
White blood count	5.50 (1.57)	8.50 (2.23)	6.22 (1.48)	0.022
Hemoglobin	12.81 (1.32)	12.20 (0.59)	12.82 (0.78)	0.461
Hematocrit	37.26 (2.79)	36.67 (2.09)	37.12 (1.79)	0.893
Platelet count	187.67 (34.96)	218.67 (25.04)	261.00 (58.01)	0.026
Neutrophil count	3.24 (1.35)	4.65 (2.15)	2.54 (0.85)	0.081
Lymphocyte count	1.57 (0.52)	2.83 (0.54)	2.91 (0.51)	< 0.001
Eosinophil count	0.18 (0.13)	0.35 (0.30)	0.26 (0.27)	0.468
Monocyte count	0.49 (0.18)	0.62 (0.40)	0.50 (0.09)	0.592
Basophil count	0.02 (0.01)	0.03 (0.01)	0.02 (0.01)	0.018
Mean corpuscular volume	69.34 (27.27)	84.10 (3.11)	80.18 (3.53)	0.288
CD4 count	512.14 (149.23)	982.83 (316.53)	1356.17 (341.70)	< 0.001
CD8 count	273.00 (59.78)	575.83 (122.98)	694.50 (185.30)	< 0.001
CD19 count	430.29 (245.38)	731.17 (270.67)	447.50 (109.80)	0.052
CD16 56	299.57 (162.19)	408.33 (276.79)	271.00 (106.84)	0.445
Naïve T cells total	495.71 (132.92)	1067.00 (376.65)	1444.83 (404.88)	< 0.001
Memory T cell total	289.29 (124.03)	492.00 (122.25)	605.83 (197.92)	0.005
Naïve helper absolute	326.14 (110.14)	732.83 (286.87)	986.33 (314.42)	< 0.001
Memory T helper abs	186.00 (88.22)	250.17 (65.13)	369.83 (95.59)	0.004
Naïve T suppressor abs	169.57 (47.62)	334.17 (101.35)	458.67 (116.10)	< 0.001
Memory T suppressor abs	103.14 (44.27)	241.67 (90.36)	236.00 (115.89)	0.016

Table 4:

Immunoglobulin levels and vaccine titers in normal and low T cell groups compared to healthy controls

Characteristic Mean (SD) or N	**22qDS with low T cell counts**	**22qDS with normal T cell counts**	**Healthy controls**	**p-value**
Immunoglobulin G	1061.71 (298.46)	954.67 (233.70)	660.67 (210.81)	0.033
Immunoglobulin A	181.06 (101.79)	136.83 (32.63)	61.15 (56.26)	0.028
Immunoglobulin M	58.14 (18.73)	50.50 (16.65)	92.00 (30.66)	0.013
Tetanus titer	0.71 (0.25)	0.50 (0.41)	1.05 (0.95)	0.308
Low Tetanus titer (<0.15) (N)	2	0	1	0.263
% of Pneumococcal titer>1.3	0.67 (0.10)	0.60 (0.26)	0.55 (0.08)	0.391
Low Pneumococcal titer (N)	3	2	5	0.142

Table 5:

Top 10 Ingenuity Canonical Pathways in T Lymphocytes from 22qDS Patients versus Controls

Ingenuity Canonical Pathways	-log(p-value)	Ratio	z-score
Communication between Innate and Adaptive Immune Cells	2.00E+01	2.32E-01	NaN
Crosstalk between Dendritic Cells and Natural Killer Cells	1.16E+01	1.69E-01	NaN
Allograft Rejection Signaling	1.08E+01	1.65E-01	NaN
Dendritic Cell Maturation	1.03E+01	9.79E-02	4.359
B Cell Receptor Signaling	1.03E+01	9.79E-02	3.317
Autoimmune Thyroid Disease Signaling	1.02E+01	2.29E-01	NaN
Phagosome Formation	9.18E+00	1.15E-01	NaN
Graft-versus-Host Disease Signaling	8.90E+00	2.08E-01	NaN
Primary Immunodeficiency Signaling	8.80E+00	2.04E-01	NaN
Neuroinflammation Signaling Pathway	7.58E+00	6.43E-02	3.9

NaN: Unable to predict

Table 6:

IPA Predicted Upstream Regulators Differentially Expressed in T Lymphocytes from 22qDS Patients versus Controls

Upstream Regulator	Log2 Fold Change	Protein Biotype	Predicted Activation State	Activation z-score	p-value of overlap
TNFSF10	0.6880	cytokine	Activated	2.7640	1.37E-10
XBP1	0.7970	transcription regulator	Activated	2.9510	0.0000097
CCL5	0.8030	cytokine	Activated	2.4880	6.98E-10
TBK1	0.8210	kinase	Activated	2.5270	2.3E-09
TNF	0.9920	cytokine	Activated	6.9390	6.62E-28
CD38	1.0670	enzyme	Activated	3.7530	1.2E-09
PTGER2	1.1280	g-protein coupled receptor	Activated	2.7240	2.99E-09
LGALS1	1.1560	other	Activated	2.1060	4.67E-10
TNFSF13B	1.3130	cytokine	Activated	2.4010	0.0000032
MAP3K8	1.5640	kinase	Activated	2.0170	0.000000259
EGR1	1.7110	transcription regulator	Activated	2.6940	2.25E-12
CD14	1.7430	transmembrane receptor	Activated	2.8050	9.81E-08
TYROBP	1.8250	transmembrane receptor	Activated	2.8970	3.85E-11
CD86	1.8480	transmembrane receptor	Activated	2.7580	2.47E-08
TLR3	1.8540	transmembrane receptor	Activated	4.5540	3.01E-25
POU2AF1	2.0370	transcription regulator	Activated	2.0990	2.52E-11
TLR4	2.3580	transmembrane receptor	Activated	4.7630	5.1E-16
PTGS2	2.4410	enzyme	Activated	3.4500	0.000000106
CD36	2.5030	transmembrane receptor	Activated	2.5990	0.00000538
FCGR2A	2.6860	transmembrane receptor	Activated	3.2660	1.02E-13
CXCL2	2.8870	cytokine	Activated	2.1290	0.00000208
S100A9	3.0460	other	Activated	3.3320	2.44E-09
IFNG	3.1580	cytokine	Activated	7.5810	1.52E-47
S100A8	3.5140	other	Activated	2.4130	5.2E-09
IL1B	3.5590	cytokine	Activated	5.8180	1.19E-27
CXCL8	3.7930	cytokine	Activated	2.4860	0.0000189
BCL6	0.9890	transcription regulator	Inhibited	-2.3080	1.95E-10
NFIL3	1.0310	transcription regulator	Inhibited	-2.2360	0.00000218

USP18	1.1050	peptidase	Inhibited	-2.3930	9.56E-08
PDCD1	1.1680	phosphatase	Inhibited	-2.2700	6.95E-14
ENTPD1	1.2040	enzyme	Inhibited	-2.2000	0.000000234
IRF4	1.2170	transcription regulator	Inhibited	-2.1650	5.24E-15

Table 7:
Top 5 Diseases and Disorders Predicted by IPA in T Lymphocytes from 22qDS Patients versus Controls

Disease and Disorder	p--value	Gene Count
Inflammatory Response	2.82E-10 - 9.95E-39	173
Immunological Disease	2.52E-10 - 2.00E-37	185
Organismal Injury and Abnormalities	3.73E-10 - 4.68E-33	299
Infectious Diseases	3.07E-10 - 1.99E-31	124
Cancer	3.66E-10 - 7.51E-30	291

Table 8:

Top 5 Molecular and Cellular Functions Predicted by IPA in T Lymphocytes from 22qDS Patients versus Control

Molecular and Cellular Function	p-value	Gene Count
Cell-To-Cell Signaling and Interaction	2.43E-10 - 3.24E-42	132
Cell Death and Survival	2.94E-10 - 1.44E-38	167
Cellular Growth and Proliferation	3.62E-10 - 1.16E-36	162
Cellular Development	3.62E-10 - 1.44E-36	153
Cellular Function and Maintenance	3.35E-10 - 2.22E-32	128

Table 9:

Top 5 Physiological System Development Functions Predicted by IPA in T Lymphocytes from 22qDS Patients versus Control

Physiological System Development Function	p-value	Gene Count	Average Activation Score
Hematological System Development and Function	3.45E-10 - 1.10E-43	160	1.5606
Tissue Morphology	3.45E-10 - 1.10E-43	119	3.0430
Immune Cell Trafficking	2.82E-10 - 9.95E-39	103	2.7454
Lymphoid Tissue Structure and Development	3.45E-10 - 1.16E-36	118	1.9080
Humoral Immune Response	3.45E-10 - 1.96E-30	82	1.1889

Table 10:

Top 10 KEGG Pathways Enriched in T Lymphocytes from 22qDS Patients versus Control Samples

KEGG Pathway Term	Gene Count	P-value	Fold Enrichment	FDR
hsa05322: Systemic lupus erythematosus	24	6.67E-15	8.1422	8.08E-12
hsa05332: Graft-versus-host disease	11	1.11E-09	15.1535	1.35E-06
hsa04940: Type I diabetes mellitus	11	1.49E-08	11.9063	1.81E-05
hsa04064:NF-kappa B signaling pathway	14	3.93E-08	7.3155	4.77E-05
hsa05330: Allograft rejection	10	6.61E-08	12.2866	8.02E-05
hsa05144: Malaria	10	8.72E-07	9.2777	0.0010587
hsa05323: Rheumatoid arthritis	12	2.84E-06	6.1992	0.00344872
hsa05164: Influenza A	16	5.19E-06	4.1803	0.00629365
hsa05034: Alcoholism	16	6.40E-06	4.1094	0.00777074
hsa05321:Inflammatory bowel disease (IBD)	10	8.84E-06	7.1032	0.01073226

Table 11:

Top 10 Biological Processes Enriched in T Lymphocytes from 22qDS Patients versus Control Samples

GO- Biological Process Term	Gene Count	P-value	Fold Enrichment	FDR
GO:0006955~immune response	36	2.07E-15	5.2214	3.608E-12
GO:0006954~inflammatory response	31	8.53E-13	4.9945	1.460E-09
GO:0006915~apoptotic process	33	9.83E-10	3.5539	1.683E-06
GO:0060333~interferon-gamma-mediated signaling pathway	12	1.92E-08	10.3203	3.294E-05
GO:0006334~nucleosome assembly	14	7.32E-08	7.1837	1.254E-04
GO:0051607~defense response to virus	16	8.60E-08	5.9211	1.474E-04
GO:0031663~lipopolysaccharide-mediated signaling pathway	8	6.77E-07	15.2655	1.160E-03
GO:0042346~positive regulation of NF-kappa B import into nucleus	7	7.89E-07	20.3539	1.352E-03
GO:0060337~type I interferon signaling pathway	10	9.04E-07	9.5409	1.548E-03
GO:0030593~neutrophil chemotaxis	10	1.18E-06	9.2518	2.022E-03

Table 12:

Top 10 Cellular Components Enriched in T Lymphocytes from 22qDS Patients versus Control Samples

Cellular Component Term	Gene Count	P-value	Fold Enrichment	FDR
GO:0000788~nuclear nucleosome	12	5.08E-11	17.5006	6.741E-08
GO:0009897~external side of plasma membrane	21	1.40E-10	6.3265	1.855E-07
GO:0000786~nucleosome	15	1.97E-10	10.2397	2.620E-07
GO:0070062~extracellular exosome	85	7.55E-10	1.9404	1.002E-06
GO:0005615~extracellular space	48	1.30E-07	2.2866	1.722E-04
GO:0009986~cell surface	26	1.33E-06	3.0782	1.761E-03
GO:0005576~extracellular region	49	8.26E-06	1.9530	1.096E-02
GO:0005829~cytosol	81	1.86E-05	1.5679	2.475E-02
GO:0042613~MHC class II protein complex	5	3.34E-04	14.5839	4.424E-01
GO:0005913~cell-cell adherens junction	15	5.53E-04	2.9800	7.312E-01

Table 13:

Top 10 Molecular Functions Enriched in T Lymphocytes from 22qDS Patients versus Control

GO- Molecular Function Term	Gene Count	P-value	Fold Enrichment	FDR
GO:0005515~protein binding	185	4.48E-08	1.3118	6.355E-05
GO:0004872~receptor activity	14	4.87E-05	4.0188	6.911E-02
GO:0046982~protein heterodimerization activity	20	1.85E-04	2.6792	2.623E-01
GO:0042605~peptide antigen binding	5	9.68E-04	11.1235	1.365E+00
GO:0042802~identical protein binding	25	9.86E-04	2.0792	1.389E+00
GO:0032395~MHC class II receptor activity	4	1.60E-03	16.6111	2.241E+00
GO:0023026~MHC class II protein complex binding	4	1.94E-03	15.5729	2.719E+00
GO:0004672~protein kinase activity	15	2.00E-03	2.6027	2.797E+00
GO:0019863~IgE binding	3	2.47E-03	37.3749	3.445E+00
GO:0030246~carbohydrate binding	10	4.34E-03	3.1781	5.985E+00

Table 14:

Top 10 Ingenuity Canonical Pathways in T Lymphocytes from 22qDS Patients with Low T Cell Counts Versus 22qDS Patients with Normal T Cell Counts

Ingenuity Canonical Pathways	-log(p-value)	Ratio	z-score
LXR/RXR Activation	6.42E+00	5.79E-02	-1.89
Osteoarthritis Pathway	4.80E+00	3.30E-02	NaN
Communication between Innate and Adaptive Immune Cells	4.51E+00	5.26E-02	NaN
GADD45 Signaling	4.31E+00	1.58E-01	NaN
Dendritic Cell Maturation	4.02E+00	3.09E-02	1.633
Crosstalk between Dendritic Cells and Natural Killer Cells	3.44E+00	4.49E-02	NaN
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	3.07E+00	2.58E-02	2.236
Role of IL-17A in Psoriasis	2.97E+00	1.54E-01	NaN
Role of CHK Proteins in Cell Cycle Checkpoint Control	2.88E+00	5.26E-02	NaN
Atherosclerosis Signaling	2.86E+00	3.15E-02	NaN

NaN: Unable to predict

Figures:

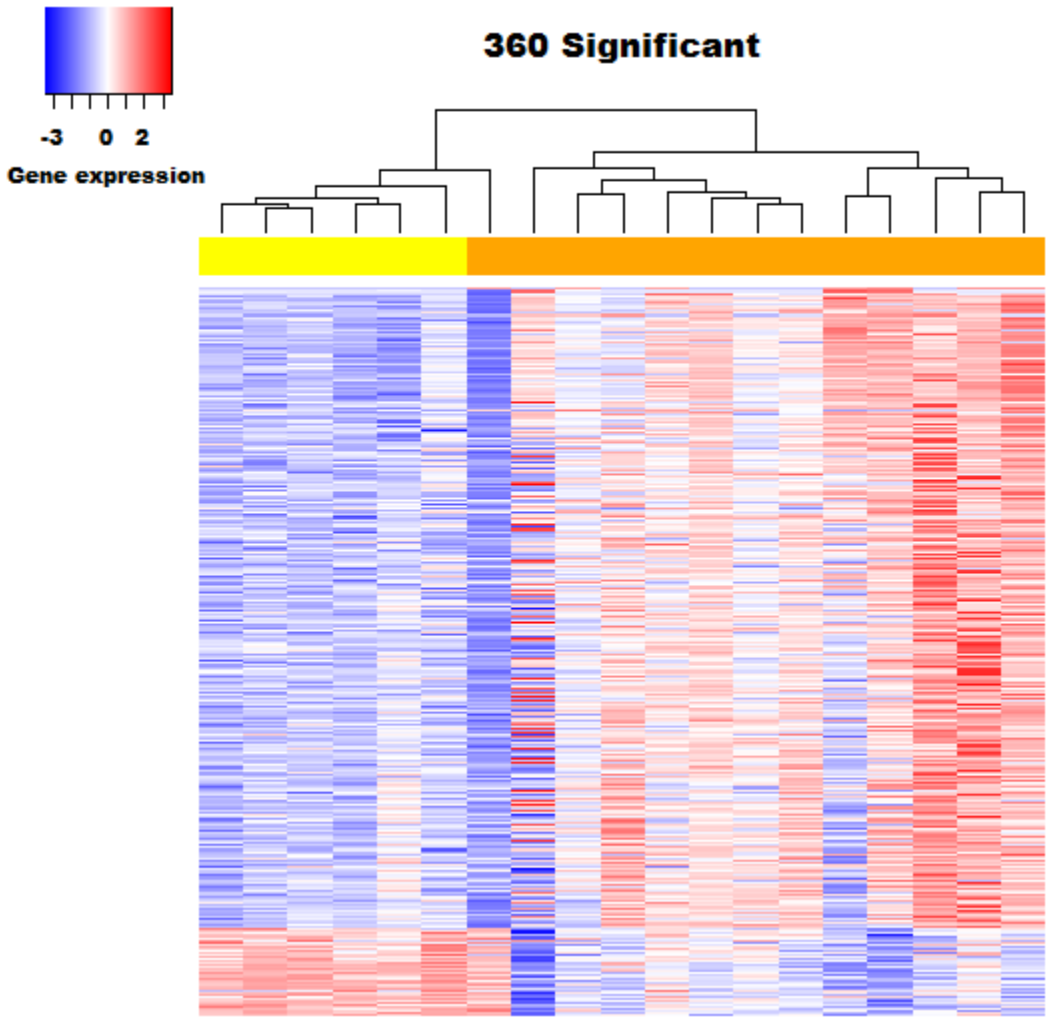

Figure 1: Heat Map of 360 differentially expressed genes in 22qDS and healthy controls.
The heat map shows log2 FPKM for 360 genes noted in the rows for 19 participants in columns. Expression of all 360 genes showed differential expression ($q<0.05$). Red indicates high expression and blue indicates low expression. 22qDS patients show distinct gene expression compared to healthy controls.

Yellow= Healthy Controls
Orange= 22qDS participants

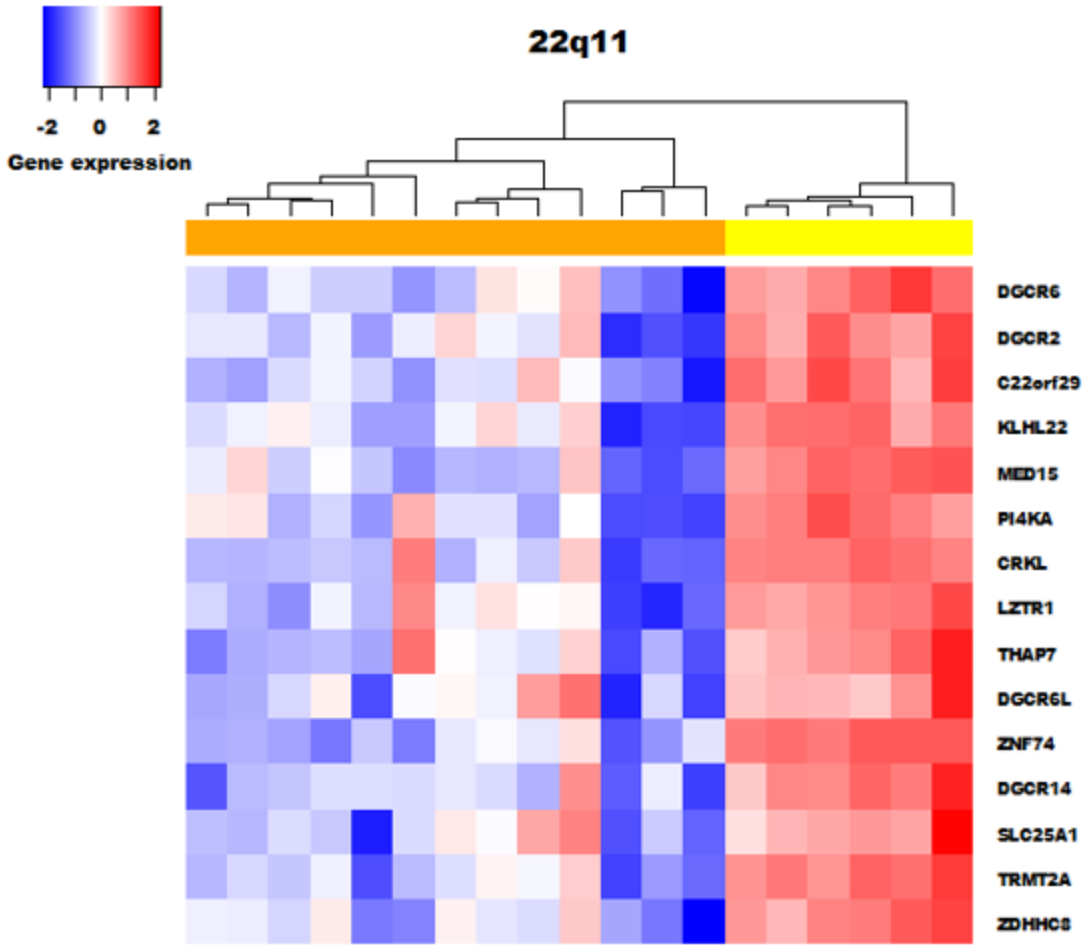

Figure 2: Heat Map of genes in 22q critical region for 22qDS patients versus healthy controls.
The heat map shows log2 FPKM for 15 genes noted in the rows for 19 subjects in columns. Expression of all 15 genes showed differential expression ($q<0.05$) in 22qDS patients compared to healthy controls. Red indicates high expression and blue indicates low expression.

Yellow= Healthy Controls
Orange= 22qDS participants

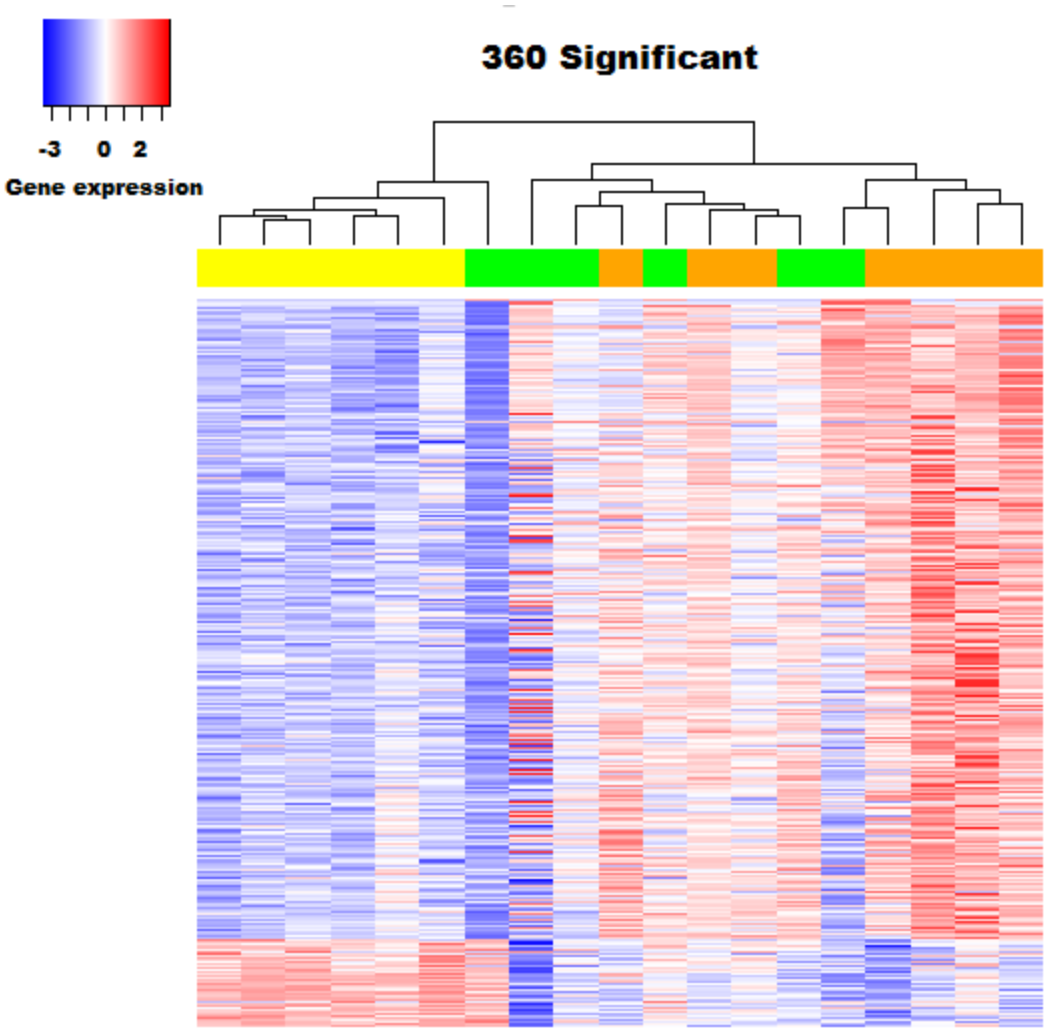

Figure 3: Heat Map of 360 genes in 22qDS with normal and low T cells compared to healthy controls.
The heat map shows log2 FPKM for 360 genes noted in the rows for 19 subjects in columns. Red indicates high expression and blue indicates low expression. 22qDS patients with low and normal T cell counts are compared here to healthy controls.

Yellow= Healthy Controls
Orange= 22qDS participants with low T cells
Green= 22qDS participants with normal T cells

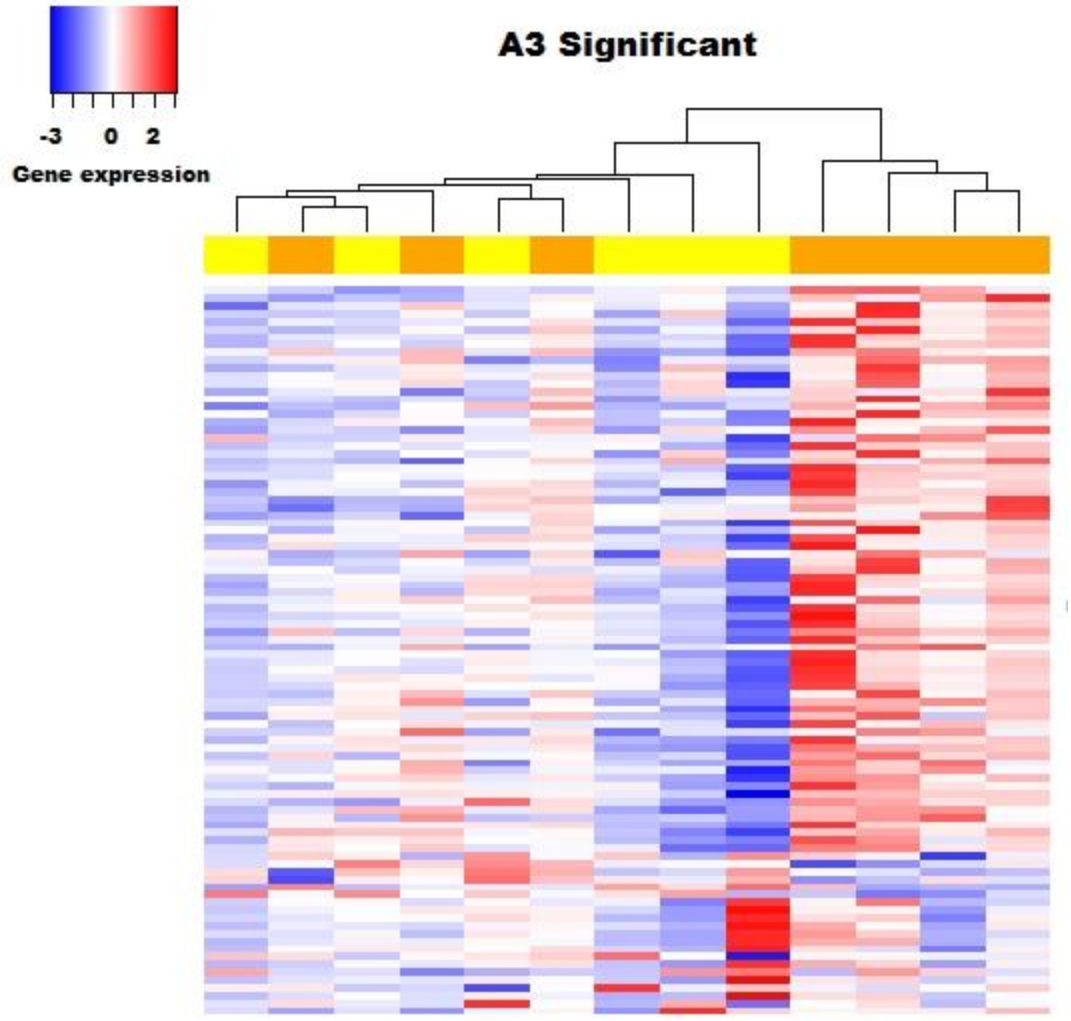

Figure 4: Heat Map of differentially expressed 94 genes in 22qDS with normal T cells versus 22qDS with low T cells.
The heat map shows log2 FPKM for 94 genes noted in the rows for 13 subjects in columns. Expression of all 15 genes showed differential expression ($q<0.05$) in 22qDS patients compared to healthy controls. Red indicates high expression and blue indicates low expression.

Yellow= 22qDS participants with normal T cells
Orange= 22qDS participants with low T cells

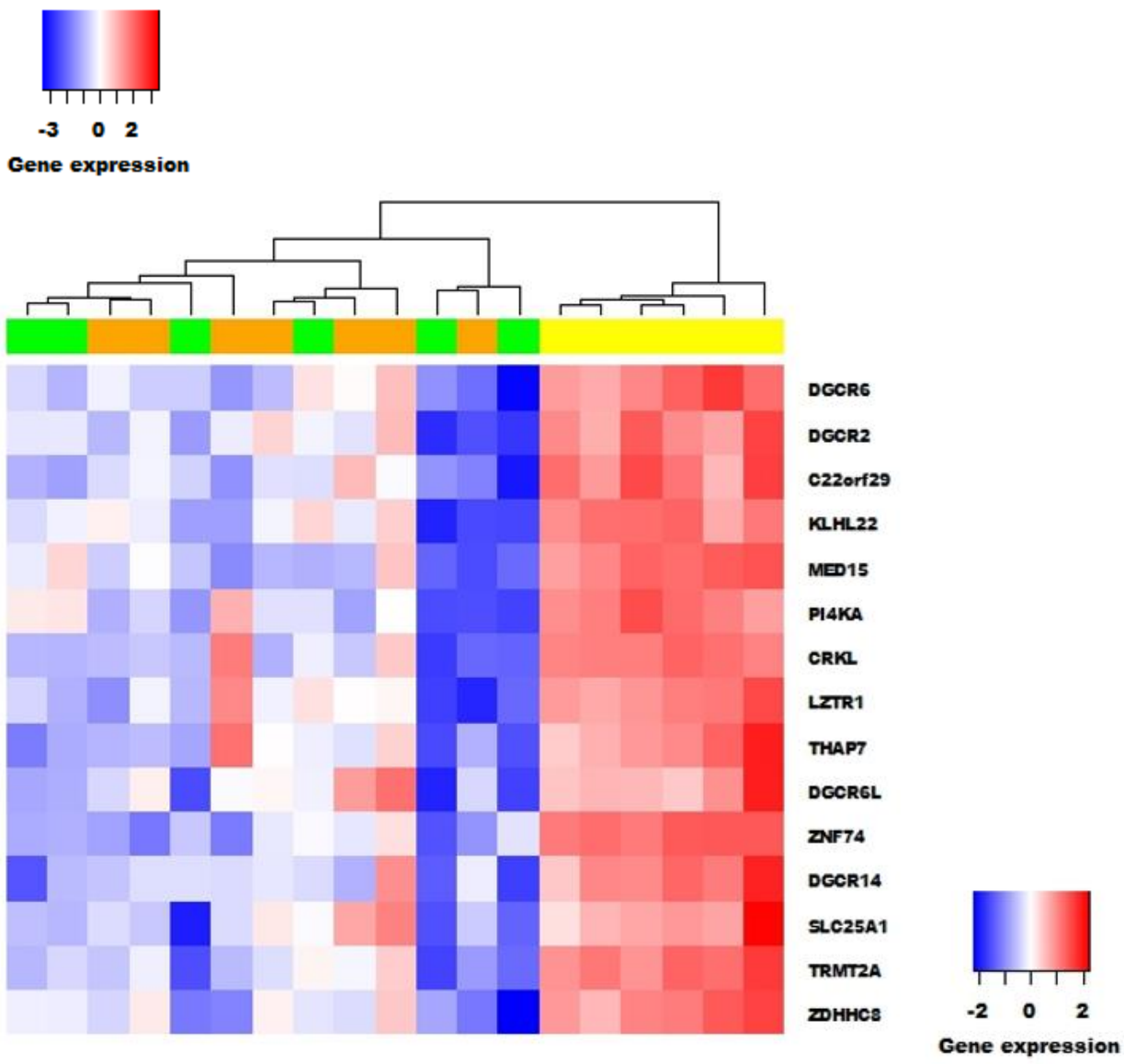

Figure 5: Heat Map of 22q genes in 22qDS with normal and low T cells compared to healthy controls
The heat map shows log2FPKM for 15 genes noted in the rows for 19 subjects in columns. Red indicates high expression and blue indicates low expression. 22qDS with normal and low T cell counts are compared to healthy controls.

Yellow= Healthy Controls
Orange= 22qDS participants with low T cells
Green= 22qDS participants with normal T cells

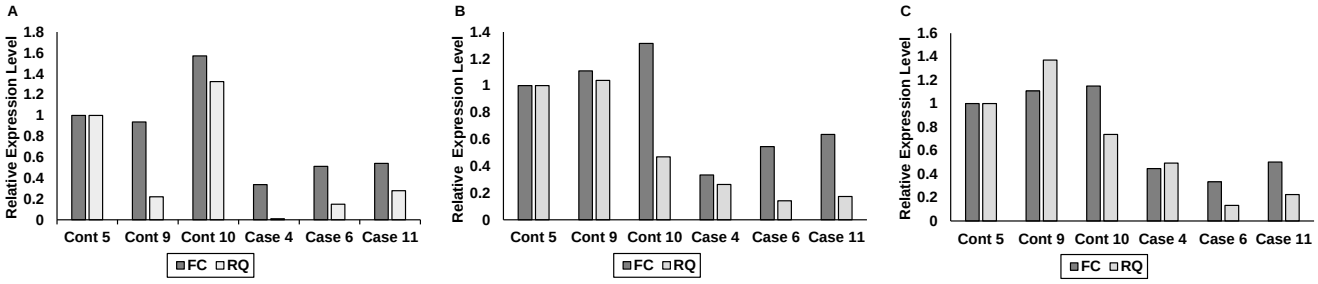

Figure 6**:** Validation of RNA sequencing by TaqMan™ gene expression analyses.

Fold Changes (FC) determined by RNA sequencing and Relative Quantification (RQ) determined by TaqMan™ quantitative PCR were compared for 3 controls and 3 22qDS patient samples for 3 genes located within the 22Q11 region: **A.** *DGCR2*, **B.** *MED15*, **C.** *TRMT2A*. FC and RQ are reported relative to control sample 5. FC was calculated by dividing the sample FPKM by the FPKM for sample 5. RQ values ($\Delta\Delta C_T$) were calculated by subtracting the mean ΔC_T for the sample 5 control group from the ΔC_T for each experimental sample. Human *ACTB* served as the endogenous control.

Chapter 7: References

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Chapter 8: Appendix

Supplemental Tables

Supplemental Table 1: Differentially Expressed Genes in T Lymphocytes from 22qDS Patients versus Control Samples

Ensembl_id	Gene Symbol	Locus	Control	22qDS	log2(fold_change)	q_value
ENSG00000211625	IGKV3D-20	2:90038847-90039479	0.0500	3.2654	6.0292	0.0041
ENSG00000211655	IGLV1-36	22:22431957-22432465	0.0500	1.5083	4.9148	0.0041
ENSG00000211973	IGHV1-69	14:106714683-106715181	0.0500	1.2603	4.6557	0.0041
ENSG00000222037	IGLC6	22:22919534-22919851	0.0500	1.6761	5.0670	0.0041
ENSG00000225523	IGKV6D-21	2:90021566-90022185	0.0500	1.4502	4.8582	0.0041
ENSG00000253998	IGKV2-29	2:89234173-89234912	0.0500	4.6329	6.5339	0.0041
ENSG00000280411	IGHV1-69-2	14:106762091-106762588	0.0500	2.4300	5.6029	0.0041
ENSG00000196565	HBG2	11:5248082-5645789	0.0169	4.5520	8.0741	0.0041
ENSG00000211892	IGHG4	14:105624340-105626066	1.0322	53.1635	5.6867	0.0041
ENSG00000211964	IGHV3-48	14:106537809-106538344	0.7523	27.7514	5.2052	0.0041
ENSG00000277632	CCL3	17:36072865-36090169	0.6581	18.8463	4.8398	0.0041
ENSG00000211651	IGLV1-44	22:22380765-22381347	1.0854	29.6989	4.7742	0.0041
ENSG00000239951	IGKV3-20	2:89142573-89143160	3.5341	87.2655	4.6260	0.0041
ENSG00000211959	IGHV4-39	14:106421710-106422218	1.0408	25.5022	4.6148	0.0041
ENSG00000241294	IGKV2-24	2:89176327-89177160	1.2092	29.4202	4.6046	0.0041
ENSG00000188536	HBA2	16:172846-173710	0.4441	10.6439	4.5830	0.0041
ENSG00000211937	IGHV2-5	14:106037901-106038365	0.9535	22.3478	4.5507	0.0041
ENSG00000270550	IGHV3-30	14:106335081-106335613	0.7881	18.0302	4.5160	0.0041
ENSG00000211896	IGHG1	14:105736342-105743071	10.0809	223.2610	4.4690	0.0041
ENSG00000244734	HBB	11:5225463-5229395	1.8615	34.5755	4.2152	0.0041
ENSG00000211947	IGHV3-21	14:106235063-106235594	1.3754	25.4104	4.2075	0.0041
ENSG00000211955	IGHV3-33	14:106359792-106360324	0.5832	9.8759	4.0820	0.0041
ENSG00000211659	IGLV3-25	22:22686725-22687271	1.3717	21.4154	3.9646	0.0041
ENSG00000243290	IGKV1-12	2:88811185-89046466	2.0139	29.5551	3.8753	0.0041
ENSG00000211675	IGLC1	22:22887779-22896107	9.5065	138.7950	3.8679	0.0041
ENSG00000244437	IGKV3-15	2:89085176-89085787	1.0080	14.4551	3.8420	0.0041
ENSG00000211945	IGHV1-18	14:106184900-106185394	1.1293	15.9560	3.8207	0.0041
ENSG00000169429	CXCL8	4:73740505-73743716	1.4944	20.7165	3.7931	0.0041
ENSG00000211592	IGKC	2:88811185-89046466	87.5943	1188.9700	3.7627	0.0041
ENSG00000132465	JCHAIN	4:70628743-70686816	13.3208	179.5500	3.7526	0.0041
ENSG00000211895	IGHA1	14:105707117-105708665	21.3793	258.2900	3.5947	0.0041
ENSG00000211677	IGLC2	22:22900975-22901437	21.3032	252.5230	3.5673	0.0041
ENSG00000125538	IL1B	2:112829750-112836903	1.8445	21.7363	3.5588	0.0041
ENSG00000278196	IGLV2-8	22:22822657-22823293	2.1096	24.2724	3.5243	0.0041
ENSG00000143546	S100A8	1:153390031-153391188	1.9572	22.3619	3.5142	0.0041
ENSG00000211949	IGHV3-23	14:106268605-106269140	4.7824	53.6420	3.4876	0.0041
ENSG00000211943	IGHV3-15	14:106153623-106154163	1.7123	19.0330	3.4745	0.0041
ENSG00000211899	IGHM	14:105854219-105856218	14.5836	161.6740	3.4707	0.0041

Ensembl_id	Gene Symbol	Locus	Control	22qDS	log2(fold_change)	q_value
ENSG00000211648	IGLV1-47	22:22357738-22358260	1.9908	21.4464	3.4293	0.0041
ENSG00000170476	MZB1	5:139387479-139390081	2.2167	22.5331	3.3456	0.0041
ENSG00000211679	IGLC3	22:22906341-22906803	19.6572	196.2510	3.3196	0.0041
ENSG00000211897	IGHG3	14:105769101-105771405	3.3471	33.1702	3.3089	0.0041
ENSG00000124772	CPNE5	6:36740774-36840002	0.1559	1.4783	3.2456	0.0041
ENSG00000163220	S100A9	1:153357853-153361027	7.7050	63.6286	3.0458	0.0041
ENSG00000248905	FMN1	15:32765544-33194733	0.4721	3.7720	2.9982	0.0041
ENSG00000211893	IGHG2	14:105643051-105649057	7.4607	57.0736	2.9355	0.0041
ENSG00000224650	IGHV3-74	14:106810441-106811131	1.3168	9.4989	2.8508	0.0041
ENSG00000211938	IGHV3-7	14:106062150-106062683	4.7230	34.0635	2.8505	0.0041
ENSG00000188906	LRRK2	12:40186008-40369285	0.1182	0.8492	2.8453	0.0041
ENSG00000211934	IGHV1-2	14:105986581-105987083	3.3461	24.0056	2.8428	0.0041
ENSG00000277443	MARCKS	6:113857361-113863471	0.1489	1.0099	2.7623	0.0041
ENSG00000211956	IGHV4-34	14:106373662-106374145	2.1312	14.3410	2.7504	0.0041
ENSG00000082438	COBLL1	2:164653623-164849334	0.1715	1.0554	2.6219	0.0041
ENSG00000105205	CLC	19:39731249-39738028	1.2973	7.8208	2.5918	0.0041
ENSG00000211673	IGLV3-1	22:22880705-22881396	4.9386	29.5898	2.5829	0.0041
ENSG00000100721	TCL1A	14:95709966-95757656	0.1586	0.9490	2.5810	0.0041
ENSG00000135218	CD36	7:80312573-80679277	0.3965	2.2481	2.5034	0.0041
ENSG00000153064	BANK1	4:101411285-102074812	0.1580	0.8959	2.5032	0.0041
ENSG00000085265	FCN1	9:134905889-134917963	1.9676	11.1504	2.5026	0.0041
ENSG00000101336	HCK	20:32052187-32101856	0.3858	2.1432	2.4738	0.0041
ENSG00000090382	LYZ	12:69348340-69354234	12.7524	69.6215	2.4488	0.0041
ENSG00000073756	PTGS2	1:186671790-186680427	0.5527	3.0008	2.4407	0.0041
ENSG00000211890	IGHA2	14:105586888-105588395	7.2989	38.6773	2.4058	0.0041
ENSG00000273983	HIST1H3G	6:26269404-26271815	1.8614	9.6549	2.3749	0.0041
ENSG00000127564	PKMYT1	16:2963943-2980539	0.2186	1.1315	2.3719	0.0041
ENSG00000136869	TLR4	9:117704331-117716871	0.2013	1.0321	2.3580	0.0041
ENSG00000131203	IDO1	8:39902274-40016391	0.3146	1.6062	2.3519	0.0041
ENSG00000078081	LAMP3	3:183122212-183163839	1.2803	6.4884	2.3414	0.0041
ENSG00000163563	MNDA	1:158831316-158849506	0.7098	3.5885	2.3380	0.0041
ENSG00000277775	HIST1H3F	6:26250194-26250605	11.9362	58.9655	2.3045	0.0041
ENSG00000038427	VCAN	5:83471464-83582303	0.6848	3.3623	2.2957	0.0041
ENSG00000163568	AIM2	1:159062483-159147096	0.4108	1.9781	2.2678	0.0041
ENSG00000239264	TXNDC5	6:7881516-8102578	8.9873	43.1250	2.2626	0.0041
ENSG00000166927	MS4A7	11:60334830-60417756	0.2660	1.2542	2.2373	0.0041
ENSG00000152217	SETBP1	18:44680172-45068510	0.4945	2.3235	2.2322	0.0041
ENSG00000100368	CSF2RB	22:36913627-36940449	0.7055	3.1024	2.1367	0.0041
ENSG00000179639	FCER1A	1:159289713-159308224	1.5310	6.7042	2.1306	0.0041
ENSG00000137801	THBS1	15:39581078-39599466	0.7100	3.0897	2.1215	0.0041
ENSG00000182985	CADM1	11:115169217-115504957	0.5664	2.3847	2.0738	0.0041
ENSG00000166503	RP11-382A20.3	15:83107406-83439445	3.3028	13.6010	2.0419	0.0041
ENSG00000110777	POU2AF1	11:111352251-111458151	0.4226	1.7341	2.0368	0.0041
ENSG00000146192	FGD2	6:37005645-37029070	0.3578	1.4500	2.0188	0.0041

Ensembl_id	Gene Symbol	Locus	Control	22qDS	log2(fold_change)	q_value
ENSG00000137959	IFI44L	1:78619921-78646145	12.9459	52.4185	2.0176	0.0041
ENSG00000135114	OASL	12:121019110-121039242	1.6754	6.5171	1.9597	0.0041
ENSG00000154451	GBP5	1:89258949-89272804	49.9322	193.5390	1.9546	0.0041
ENSG00000092853	CLSPN	1:35720217-35769967	0.3136	1.1963	1.9315	0.0041
ENSG00000101057	MYBL2	20:43667018-43716496	0.6765	2.5154	1.8946	0.0041
ENSG00000275302	CCL4	17:36103589-36105621	7.2847	26.8974	1.8845	0.0041
ENSG00000011422	PLAUR	19:43646094-43670547	1.2082	4.4574	1.8834	0.0041
ENSG00000058091	CDK14	7:90335222-91210590	0.4235	1.5435	1.8659	0.0041
ENSG00000204287	HLA-DRA	6:32439841-32445046	13.1398	47.3898	1.8506	0.0041
ENSG00000171848	RRM2	2:10122327-10131419	1.7681	6.3391	1.8420	0.0041
ENSG00000011600	TYROBP	19:35904400-35908295	3.4607	12.2575	1.8246	0.0041
ENSG00000167900	TK1	17:78174074-78187233	0.9815	3.4687	1.8213	0.0041
ENSG00000081985	IL12RB2	1:67307363-67396900	1.4812	5.1415	1.7954	0.0041
ENSG00000088325	TPX2	20:31739270-31801805	0.8091	2.7150	1.7465	0.0041
ENSG00000175063	UBE2C	20:45812575-45816957	0.8280	2.7754	1.7449	0.0041
ENSG00000173334	TRIB1	8:125430320-125438405	1.2578	4.1867	1.7349	0.0041
ENSG00000163694	RBM47	4:40423266-40630875	0.3539	1.1563	1.7080	0.0041
ENSG00000025708	TYMP	22:50523567-50532580	4.4082	14.1841	1.6860	0.0041
ENSG00000125462	C1orf61	1:156404249-156430701	0.4233	1.3565	1.6802	0.0041
ENSG00000196141	SPATS2L	2:200305880-200482263	1.7600	5.6152	1.6737	0.0041
ENSG00000115902	SLC1A4	2:64988476-65023865	1.0250	3.2027	1.6437	0.0041
ENSG00000197629	MPEG1	11:59171429-59212951	0.8146	2.5345	1.6376	0.0041
ENSG00000101439	CST3	20:23626705-23638473	3.2864	9.7753	1.5727	0.0041
ENSG00000107968	MAP3K8	10:30433936-30461833	6.8753	20.3335	1.5644	0.0041
ENSG00000184357	HIST1H1B	6:27866848-27867529	34.5908	101.6540	1.5552	0.0041
ENSG00000081189	MEF2C	5:88507545-89466398	1.0743	3.0962	1.5272	0.0041
ENSG00000057657	PRDM1	6:106086319-106109939	7.2670	20.9006	1.5241	0.0041
ENSG00000273703	HIST1H2BM	6:27815043-27815424	25.5406	71.3436	1.4820	0.0041
ENSG00000188313	PLSCR1	3:146515179-146544864	8.7901	24.5330	1.4808	0.0041
ENSG00000140105	WARS	14:100333787-100530303	11.3950	31.7324	1.4776	0.0041
ENSG00000137804	NUSAP1	15:41332693-41381050	2.9549	8.1044	1.4556	0.0041
ENSG00000274997	HIST1H2AH	6:27147128-27147516	19.4530	52.9122	1.4436	0.0041
ENSG00000007968	E2F2	1:23506429-23531220	0.9308	2.5302	1.4427	0.0041
ENSG00000148773	MKI67	10:128096658-128126385	0.9631	2.6106	1.4386	0.0041
ENSG00000275713	HIST1H2BH	6:26251650-26253710	5.6561	14.9075	1.3982	0.0041
ENSG00000160791	CCR5	3:46364954-46407059	2.6803	7.0051	1.3860	0.0041
ENSG00000274267	HIST1H3B	6:26031649-26032060	41.7061	107.2280	1.3624	0.0041
ENSG00000196747	HIST1H2AI	6:27808198-27808701	23.7834	60.9072	1.3567	0.0041
ENSG00000138166	DUSP5	10:110497837-110511544	9.0699	23.1128	1.3495	0.0041
ENSG00000126709	IFI6	1:27666060-27703063	21.9997	55.9695	1.3472	0.0041
ENSG00000121807	CCR2	3:46353733-46360928	3.7947	9.5214	1.3272	0.0041
ENSG00000276180	HIST1H4I	6:27138587-27139881	4.1193	10.3164	1.3245	0.0041
ENSG00000048052	HDAC9	7:18086948-19002416	1.3318	3.3253	1.3202	0.0041
ENSG00000131747	TOP2A	17:40388515-40417950	1.7538	4.3607	1.3141	0.0041

Ensembl_id	Gene Symbol	Locus	Control	22qDS	log2(fold_change)	q_value
ENSG00000157601	MX1	21:41420303-41459214	30.1043	72.6341	1.2707	0.0041
ENSG00000196189	SEMA4A	1:156147365-156177752	0.8586	2.0675	1.2678	0.0041
ENSG00000117228	GBP1	1:89052318-89065360	35.5110	85.5021	1.2677	0.0041
ENSG00000231389	HLA-DPA1	6:33064568-33087201	14.1728	33.7094	1.2500	0.0041
ENSG00000274641	HIST1H2BO	6:27893462-27893843	36.1791	85.7746	1.2454	0.0041
ENSG00000012124	CD22	19:35319260-35347355	0.5593	1.3241	1.2433	0.0041
ENSG00000026751	SLAMF7	1:160739056-160754821	4.9194	11.4442	1.2181	0.0041
ENSG00000137265	IRF4	6:391738-411447	6.7121	15.6042	1.2171	0.0041
ENSG00000182718	ANXA2	15:60347133-60402883	28.7439	66.6804	1.2140	0.0041
ENSG00000181847	TIGIT	3:114276912-114310288	9.5704	22.0573	1.2046	0.0041
ENSG00000152689	RASGRP3	2:33436323-33564750	1.9350	4.4538	1.2027	0.0041
ENSG00000120875	DUSP4	8:29333063-29350668	3.8560	8.7029	1.1744	0.0041
ENSG00000187608	ISG15	1:1001137-1014541	25.7382	57.8652	1.1688	0.0041
ENSG00000100342	APOL1	22:36253009-36267530	3.2319	7.2455	1.1647	0.0041
ENSG00000103811	CTSH	15:78921057-78949574	6.8604	15.3023	1.1574	0.0041
ENSG00000138160	KIF11	10:92593285-92655395	1.0911	2.4135	1.1453	0.0041
ENSG00000145649	GZMA	5:55102647-55110252	36.6889	80.8713	1.1403	0.0041
ENSG00000144354	CDCA7	2:173338218-173368997	2.3260	5.0962	1.1316	0.0041
ENSG00000125384	PTGER2	14:52314304-52328606	11.2771	24.6458	1.1280	0.0041
ENSG00000138646	HERC5	4:88457116-88506163	3.7030	8.0507	1.1204	0.0041
ENSG00000184979	USP18	22:18149898-18177397	2.6609	5.7220	1.1046	0.0041
ENSG00000115956	PLEK	2:68361213-68397453	10.1537	21.8230	1.1038	0.0041
ENSG00000109189	USP46	4:52590971-52659335	2.7394	5.8221	1.0877	0.0041
ENSG00000196890	HIST3H2BB	1:228458106-228460470	2.3894	5.0602	1.0826	0.0041
ENSG00000196126	HLA-DRB1	6:32552712-32589848	8.5133	17.8496	1.0681	0.0041
ENSG00000004468	CD38	4:15778274-15853230	6.5425	13.7061	1.0669	0.0041
ENSG00000105374	NKG7	19:51371605-51372715	64.3295	133.3370	1.0515	0.0041
ENSG00000111885	MAN1A1	6:119177208-119349761	5.5016	11.3856	1.0493	0.0041
ENSG00000180644	PRF1	10:70597347-70602775	37.4144	77.3516	1.0478	0.0041
ENSG00000134107	BHLHE40	3:4896808-4985323	12.0523	24.8948	1.0465	0.0041
ENSG00000185130	HIST1H2BL	6:27807443-27807931	27.1880	54.1698	0.9945	0.0041
ENSG00000169554	ZEB2	2:144384080-144524583	11.2221	22.2911	0.9901	0.0041
ENSG00000124256	ZBP1	20:57603845-57620576	8.5085	16.8586	0.9865	0.0041
ENSG00000137965	IFI44	1:78649795-78664078	19.2504	38.1422	0.9865	0.0041
ENSG00000113088	GZMK	5:54977863-55042844	25.3233	49.1053	0.9554	0.0041
ENSG00000168329	CX3CR1	3:39263493-39281735	6.4381	12.3294	0.9374	0.0041
ENSG00000124635	HIST1H2BJ	6:27125896-27132750	43.5586	83.2533	0.9346	0.0041
ENSG00000183508	FAM46C	1:117605933-117628372	15.7367	29.9653	0.9292	0.0041
ENSG00000112149	CD83	6:14117255-14136918	4.3716	8.2503	0.9163	0.0041
ENSG00000077984	CST7	20:24949229-24959928	30.3951	57.3340	0.9156	0.0041
ENSG00000152778	IFIT5	10:89414585-89421001	8.3304	15.5442	0.8999	0.0041
ENSG00000019582	CD74	5:150401636-150412929	107.3050	198.5560	0.8878	0.0041
ENSG00000158470	B4GALT5	20:49632944-49713878	2.5480	4.6865	0.8792	0.0041
ENSG00000122862	SRGN	10:69088105-69104811	125.2920	228.2850	0.8655	0.0041

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ENSG00000164111	ANXA5	4:121667954-121697113	21.5964	38.8332	0.8465	0.0041
ENSG00000163191	S100A11	1:151994530-152047907	33.0269	58.5247	0.8254	0.0041
ENSG00000155090	KLF10	8:102648778-102655902	5.9637	10.5269	0.8198	0.0041
ENSG00000135916	ITM2C	2:230864638-230879248	10.6745	18.7934	0.8161	0.0041
ENSG00000132718	SYT11	1:155859508-155885199	3.3020	5.8063	0.8143	0.0041
ENSG00000271503	CCL5	17:35868966-35885863	89.7325	156.5460	0.8029	0.0041
ENSG00000100219	XBP1	22:28794554-28800597	53.1673	92.3884	0.7972	0.0041
ENSG00000103257	SLC7A5	16:87830022-87869488	3.5812	6.2074	0.7935	0.0041
ENSG00000196154	S100A4	1:153543612-153550136	143.6550	248.8010	0.7924	0.0041
ENSG00000213719	CLIC1	6:31727037-31739763	60.1406	103.5060	0.7833	0.0041
ENSG00000130066	SAT1	X:23783172-23786226	68.8415	118.0430	0.7780	0.0041
ENSG00000163564	PYHIN1	1:158930795-158977054	25.2562	42.1452	0.7387	0.0041
ENSG00000197442	MAP3K5	6:136557046-136792518	7.3816	12.1183	0.7152	0.0041
ENSG00000023445	BIRC3	11:102317449-102339403	54.4528	82.5738	0.6007	0.0041
ENSG00000173114	LRRN3	7:110663050-111562517	39.1070	23.4597	-0.7372	0.0041
ENSG00000072110	ACTN1	14:68874142-68979440	59.0795	35.3507	-0.7409	0.0041
ENSG00000105193	RPS16	19:39433206-39435948	588.5610	329.0340	-0.8390	0.0041
ENSG00000275342	SGK223	8:8317735-8386498	5.8990	3.2062	-0.8796	0.0041
ENSG00000183691	NOG	17:56593698-56595590	21.9303	11.6839	-0.9084	0.0041
ENSG00000142102	ATHL1	11:289134-296107	227.0740	119.5770	-0.9252	0.0041
ENSG00000255026	RP11-326C3.2	11:287304-288987	226.2790	116.8210	-0.9538	0.0041
ENSG00000135960	EDAR	2:108894470-108989372	7.6107	3.8915	-0.9677	0.0041
ENSG00000184436	THAP7	22:20999103-21045017	23.7407	12.0162	-0.9824	0.0041
ENSG00000099942	CRKL	22:20917425-20953749	18.5206	9.1256	-1.0211	0.0041
ENSG00000241973	PI4KA	22:20707690-20891218	36.0230	16.6493	-1.1135	0.0041
ENSG00000099949	LZTR1	22:20965107-20999038	29.3427	13.5571	-1.1140	0.0041
ENSG00000070413	DGCR2	22:19036281-19128449	21.5272	9.8128	-1.1334	0.0041
ENSG00000166341	DCHS1	11:6621322-6655854	4.7385	2.1512	-1.1393	0.0041
ENSG00000099917	MED15	22:20495912-20592218	37.2456	16.2153	-1.1997	0.0041
ENSG00000099910	KLHL22	22:20424584-20495883	16.6921	7.1298	-1.2272	0.0041
ENSG00000124766	SOX4	6:21592768-21598619	6.9498	2.9134	-1.2543	0.0041
ENSG00000215012	C22orf29	22:19756702-19854939	5.5946	2.3253	-1.2666	0.0041
ENSG00000261150	EPPK1	8:143857323-143878464	1.9516	0.7788	-1.3253	0.0041
ENSG00000158966	CACHD1	1:64470791-64693058	2.5939	1.0310	-1.3310	0.0041
ENSG00000172915	NBEA	13:34942286-35673022	2.0959	0.8096	-1.3723	0.0041
ENSG00000275395	FCGBP	19:39863322-39934626	4.3693	1.6249	-1.4270	0.0041
ENSG00000183628	DGCR6	22:18906027-18936553	2.3158	0.6620	-1.8067	0.0041
ENSG00000254681	PKD1P5	16:18358085-18401940	1.0069	0.2390	-2.0747	0.0041
ENSG00000249835	VCAN-AS1	5:83471464-83582303	0.0500	1.1547	4.5294	0.0071
ENSG00000211663	IGLV3-19	22:22720622-22721145	0.7819	21.0279	4.7492	0.0071
ENSG00000211662	IGLV3-21	22:22711688-22713203	1.4850	19.7766	3.7352	0.0071
ENSG00000186818	LILRB4	19:54643888-54670359	0.1270	1.4685	3.5319	0.0071
ENSG00000197249	SERPINA1	14:94376746-94390693	0.5596	4.6937	3.0682	0.0071
ENSG00000095585	BLNK	10:96129714-96271587	0.1497	1.0889	2.8630	0.0071

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ENSG00000113140	SPARC	5:151661095-151724782	0.1938	1.3216	2.7699	0.0071
ENSG00000149516	MS4A3	11:60056586-60071128	0.2361	1.5607	2.7246	0.0071
ENSG00000124882	EREG	4:74365142-74388751	0.1249	0.7929	2.6665	0.0071
ENSG00000121316	PLBD1	12:14503660-14757963	0.2415	1.4420	2.5781	0.0071
ENSG00000121380	BCL2L14	12:12049843-12267012	0.5058	2.9621	2.5500	0.0071
ENSG00000185215	TNFAIP2	14:103123441-103137439	0.7581	3.4588	2.1897	0.0071
ENSG00000169504	CLIC4	1:24745356-24844324	0.3481	1.1665	1.7444	0.0071
ENSG00000100453	GZMB	14:24595722-24657774	9.3501	30.6488	1.7128	0.0071
ENSG00000141574	SECTM1	17:82321023-82334074	0.8263	2.7030	1.7098	0.0071
ENSG00000172243	CLEC7A	12:10116776-10130258	0.5899	1.8517	1.6503	0.0071
ENSG00000276368	HIST1H2AJ	6:27814353-27814740	6.5749	20.4634	1.6380	0.0071
ENSG00000124762	CDKN1A	6:36676459-36687339	1.5345	4.0330	1.3941	0.0071
ENSG00000131981	LGALS3	14:55124109-55145413	2.0943	5.4987	1.3927	0.0071
ENSG00000135604	STX11	6:144150525-144188370	1.9607	5.0652	1.3693	0.0071
ENSG00000185432	METTL7A	12:50923471-50932517	1.4003	3.4096	1.2839	0.0071
ENSG00000100097	LGALS1	22:37675607-37679806	23.2048	51.7088	1.1560	0.0071
ENSG00000066279	ASPM	1:197084127-197146694	0.5043	1.1069	1.1341	0.0071
ENSG00000165030	NFIL3	9:91409044-91423862	2.8327	5.7904	1.0315	0.0071
ENSG00000178573	MAF	16:79585842-79600714	11.0072	21.2543	0.9493	0.0071
ENSG00000225783	MIAT	22:26646427-26780207	10.0390	18.5424	0.8852	0.0071
ENSG00000135842	FAM129A	1:184790723-184974550	7.6389	12.5913	0.7210	0.0071
ENSG00000028137	TNFRSF1B	1:12166942-12209228	17.0743	27.7693	0.7017	0.0071
ENSG00000143870	PDIA6	2:10721648-10837977	21.4315	34.3926	0.6824	0.0071
ENSG00000128185	DGCR6L	22:20314275-20320080	17.2326	9.4591	-0.8654	0.0071
ENSG00000172985	SH3RF3	2:109129347-109504632	1.9340	0.8753	-1.1437	0.0071
ENSG00000185252	ZNF74	22:20394114-20408461	3.4167	1.4429	-1.2436	0.0071
ENSG00000211653	IGLV1-40	22:22409765-22410282	0.6655	21.6368	5.0230	0.0099
ENSG00000240864	IGKV1-16	2:89099858-89100361	1.1918	11.6812	3.2930	0.0099
ENSG00000081041	CXCL2	4:74097034-74099293	0.2510	1.8565	2.8871	0.0099
ENSG00000120738	EGR1	5:138465489-138469315	0.4258	1.3939	1.7108	0.0099
ENSG00000254087	LYN	8:55879812-56014168	1.2046	3.4037	1.4985	0.0099
ENSG00000237649	KIFC1	6:33391535-33409924	0.6919	1.8495	1.4186	0.0099
ENSG00000271303	SRXN1	20:646614-676179	1.1417	2.8795	1.3347	0.0099
ENSG00000133106	EPSTI1	13:42886387-42992271	16.8067	41.8902	1.3176	0.0099
ENSG00000026103	FAS	10:88879733-89015785	11.9024	27.3956	1.2027	0.0099
ENSG00000143878	RHOB	2:20447073-20449445	2.6206	5.3808	1.0379	0.0099
ENSG00000232810	TNF	6:31575566-31578336	3.2021	6.3685	0.9920	0.0099
ENSG00000148175	STOM	9:121338987-121370304	18.9761	36.8037	0.9557	0.0099
ENSG00000183735	TBK1	12:64451590-64502108	5.8204	10.2847	0.8213	0.0099
ENSG00000137441	FGFBP2	4:15960242-16084378	17.0784	29.9169	0.8088	0.0099
ENSG00000140030	GPR65	14:88005123-88015611	7.2508	12.1923	0.7498	0.0099
ENSG00000198833	UBE2J1	6:89326624-89352848	11.5381	17.7508	0.6215	0.0099
ENSG00000100056	DGCR14	22:19130278-19144684	8.4338	4.0302	-1.0653	0.0099
ENSG00000211649	IGLV7-46	22:22369613-22370087	0.7892	7.6287	3.2731	0.0126

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ENSG00000143226	FCGR2A	1:161505429-161605662	0.3631	2.3364	2.6859	0.0126
ENSG00000244682	FCGR2C	1:161505429-161605662	0.4583	1.7735	1.9521	0.0126
ENSG00000114013	CD86	3:122055365-122121139	0.2956	1.0637	1.8476	0.0126
ENSG00000165025	SYK	9:90801786-90898549	0.5199	1.8007	1.7923	0.0126
ENSG00000010671	BTK	X:101349446-101390796	0.7737	2.1961	1.5052	0.0126
ENSG00000115604	IL18R1	2:102311501-102398775	3.8404	8.5447	1.1538	0.0126
ENSG00000095794	CREM	10:35098005-35212958	20.0678	37.0251	0.8836	0.0126
ENSG00000177409	SAMD9L	7:93130054-93148369	25.9777	47.1041	0.8586	0.0126
ENSG00000185947	ZNF267	16:31873757-31917357	16.7216	26.7648	0.6786	0.0126
ENSG00000185477	GPRIN3	4:89236385-89308010	13.8953	22.0950	0.6691	0.0126
ENSG00000069188	SDK2	17:73334383-73644089	1.6142	0.5351	-1.5930	0.0126
ENSG00000211666	IGLV2-14	22:22758695-22759218	10.0151	68.2969	2.7696	0.0152
ENSG00000162772	ATF3	1:212565333-212620777	0.2752	0.9479	1.7845	0.0152
ENSG00000168461	RAB31	18:9708164-9862551	0.4497	1.5124	1.7499	0.0152
ENSG00000089692	LAG3	12:6772511-6778455	1.1247	2.9628	1.3975	0.0152
ENSG00000125810	CD93	20:23079348-23086340	0.5902	1.2469	1.0791	0.0152
ENSG00000180739	S1PR5	19:10512741-10517931	6.4269	11.8387	0.8813	0.0152
ENSG00000162645	GBP2	1:89106131-89176040	83.1548	135.4800	0.7042	0.0152
ENSG00000150347	ARID5B	10:61901299-62096944	14.5992	23.7656	0.7030	0.0152
ENSG00000111796	KLRB1	12:9594550-9607886	38.0867	60.4412	0.6662	0.0152
ENSG00000100075	SLC25A1	22:19175574-19178830	9.3079	4.8465	-0.9415	0.0152
ENSG00000118200	CAMSAP2	1:200739557-200860704	3.1486	1.6281	-0.9515	0.0152
ENSG00000179348	GATA2	3:128479426-128502348	0.6157	1.8342	1.5750	0.0182
ENSG00000211942	IGHV3-13	14:106129539-106130072	0.5069	6.8261	3.7513	0.0207
ENSG00000110077	MS4A6A	11:60172013-60184666	1.0060	3.9598	1.9768	0.0207
ENSG00000188389	PDCD1	2:241849880-241858908	1.7713	3.9793	1.1677	0.0207
ENSG00000113916	BCL6	3:187698258-187745727	4.3812	8.6982	0.9894	0.0207
ENSG00000111640	GAPDH	12:6533926-6538374	194.3080	314.0420	0.6926	0.0207
ENSG00000171314	PGAM1	10:97426159-97433441	34.8841	53.8446	0.6262	0.0207
ENSG00000074800	ENO1	1:8861001-8879894	156.7530	230.0290	0.5533	0.0207
ENSG00000134321	RSAD2	2:6840569-6898239	4.6603	13.6284	1.5481	0.0234
ENSG00000121858	TNFSF10	3:172505507-172523507	17.8996	28.8355	0.6879	0.0234
ENSG00000106123	EPHB6	7:142855060-142871094	11.8690	7.3164	-0.6980	0.0234
ENSG00000140287	HDC	15:50241946-50266026	0.7987	2.8135	1.8166	0.0258
ENSG00000042980	ADAM28	8:24294039-24912073	0.3163	1.0279	1.7003	0.0258
ENSG00000138185	ENTPD1	10:95711778-96090238	1.4783	3.4046	1.2035	0.0258
ENSG00000116663	FBXO6	1:11664123-11674354	2.1286	4.7567	1.1600	0.0258
ENSG00000096060	FKBP5	6:35573584-35728583	25.7953	17.1402	-0.5897	0.0258
ENSG00000099899	TRMT2A	22:20080231-20127357	29.1859	12.8691	-1.1814	0.0258
ENSG00000253701	AL928768.3	14:105703960-105704602	0.7464	6.0127	3.0100	0.0278
ENSG00000211638	IGLV8-61	22:22098699-22099212	0.9972	12.6380	3.6638	0.0278
ENSG00000216490	IFI30	19:18153117-18178117	1.8033	13.3053	2.8833	0.0278
ENSG00000170456	DENND5B	12:31382222-31615666	0.1787	0.8679	2.2796	0.0278
ENSG00000164611	PTTG1	5:160421821-160428744	4.6629	10.9927	1.2373	0.0278

Ensembl_id	Gene Symbol	Locus	Control	22qDS	log2(fold_change)	q_value
ENSG00000169679	BUB1	2:110637697-110678114	1.6701	3.6877	1.1428	0.0278
ENSG00000204525	HLA-C	6:31268748-31272130	430.9390	694.6020	0.6887	0.0278
ENSG00000132646	PCNA	20:5114952-5126626	18.8706	30.2268	0.6797	0.0278
ENSG00000100599	RIN3	14:92513773-92688994	17.9333	11.6893	-0.6175	0.0278
ENSG00000210184	MT-TS2	MT:12206-12265	0.0500	2611.2100	15.6724	0.0300
ENSG00000243238	IGKV2-30	2:89244780-89245596	0.5169	10.9298	4.4022	0.0300
ENSG00000163421	PROK2	3:71771655-71785206	0.3284	1.7285	2.3962	0.0300
ENSG00000164342	TLR3	4:186069151-186088069	0.5964	2.1564	1.8543	0.0300
ENSG00000147889	CDKN2A	9:21802542-22121097	0.5243	1.5065	1.5228	0.0300
ENSG00000138642	HERC6	4:88378738-88443111	10.3681	20.9503	1.0148	0.0300
ENSG00000254709	IGLL5	22:22887779-22896107	0.4970	15.5978	4.9719	0.0322
ENSG00000156738	MS4A1	11:60455751-60470760	0.9764	2.9069	1.5739	0.0322
ENSG00000197943	PLCG2	16:81738247-81962693	1.8690	3.7684	1.0117	0.0322
ENSG00000164938	TP53INP1	8:94813310-95116455	9.6359	17.6625	0.8742	0.0322
ENSG00000008283	CYB561	17:63432303-63446378	3.8411	6.7271	0.8085	0.0322
ENSG00000170458	CD14	5:140631727-140633701	0.7030	2.3532	1.7429	0.0343
ENSG00000120708	TGFBI	5:136028894-136063818	0.8587	2.0176	1.2323	0.0343
ENSG00000279602	CTD-3014M21.1	17:43360040-43361361	11.4738	19.1089	0.7359	0.0343
ENSG00000266714	MYO15B	17:75588057-75626501	68.9479	40.3509	-0.7729	0.0343
ENSG00000165730	STOX1	10:68827540-68895432	1.5359	0.6160	-1.3181	0.0343
ENSG00000111537	IFNG	12:67989444-68234686	1.8359	16.3822	3.1576	0.0362
ENSG00000275063	AC233755.1	KI270726.1:41443-41876	1.3047	5.7947	2.1511	0.0362
ENSG00000178999	AURKB	17:8204732-8210600	0.8844	2.6140	1.5635	0.0362
ENSG00000011426	ANLN	7:36324220-36453791	0.5105	1.3125	1.3623	0.0362
ENSG00000169252	ADRB2	5:148825244-148828687	3.4687	5.9915	0.7885	0.0362
ENSG00000156587	UBE2L6	11:57551655-57568284	39.4837	62.4158	0.6607	0.0362
ENSG00000099904	ZDHHC8	22:20129455-20148007	11.3579	4.4448	-1.3535	0.0362
ENSG00000141682	PMAIP1	18:59899947-59904306	7.7790	13.8234	0.8295	0.0384
ENSG00000185697	MYBL1	8:66562174-66614247	11.9727	19.5937	0.7106	0.0384
ENSG00000163659	TIPARP	3:156671861-156706770	28.5470	44.8701	0.6524	0.0384
ENSG00000279346	AC104389.1	11:5248082-5645789	0.0500	6.5839	7.0409	0.0406
ENSG00000262655	SPON1	11:13962688-14273691	1.7086	3.7717	1.1424	0.0406
ENSG00000277224	HIST1H2BF	6:26199519-26200715	20.0416	33.0661	0.7224	0.0406
ENSG00000211935	IGHV1-3	14:106005094-106005574	1.5501	9.6544	2.6389	0.0421
ENSG00000089127	OAS1	12:112906776-113017751	6.1560	21.6080	1.8115	0.0421
ENSG00000169413	RNASE6	14:20781050-20782467	0.7441	2.1891	1.5568	0.0421
ENSG00000113070	HBEGF	5:140332842-140346631	0.4526	1.3274	1.5522	0.0421
ENSG00000102524	TNFSF13B	13:108251239-108308484	1.4971	3.7204	1.3133	0.0421
ENSG00000279296	RP11-609D21.3	17:6755446-6776116	17.0577	32.9619	0.9504	0.0421
ENSG00000162576	MXRA8	1:1352688-1361777	7.0846	3.2708	-1.1151	0.0421
ENSG00000134909	ARHGAP32	11:128965059-129279324	4.6266	1.9794	-1.2249	0.0421
ENSG00000278828	HIST1H3H	6:27810063-27811300	29.1941	46.4606	0.6703	0.0445
ENSG00000048462	TNFRSF17	16:11927372-11976643	0.6123	4.1376	2.7565	0.0462
ENSG00000149534	MS4A2	11:60088260-60098466	0.2231	1.0635	2.2532	0.0462

Ensembl_id	Gene Symbol	Locus	Control	22qDS	log2(fold_change)	q_value
ENSG00000150681	RGS18	1:192158456-192185815	0.6487	1.7241	1.4103	0.0462
ENSG00000203747	FCGR3A	1:161505429-161605662	3.7791	8.4620	1.1630	0.0462
ENSG00000188933	USP32P1	17:16689536-16816540	7.5346	3.1603	-1.2535	0.0462
ENSG00000182489	XKRX	X:100913444-100929433	1.0395	0.3047	-1.7703	0.0462
ENSG00000211660	IGLV2-23	22:22697788-22698407	2.8519	15.6935	2.4602	0.0478
ENSG00000261438	RP11-399O19.9	10:89015835-89017059	0.4697	1.3804	1.5554	0.0478
ENSG00000134690	CDCA8	1:37692417-37709719	0.3618	1.0345	1.5154	0.0478
ENSG00000189057	FAM111B	11:59107184-59127410	0.4321	1.1601	1.4249	0.0478
ENSG00000100376	FAM118A	22:45308967-45341955	70.1234	40.1456	-0.8047	0.0478
ENSG00000174807	CD248	11:66312852-66319237	4.3432	2.2749	-0.9330	0.0478
ENSG00000182022	CHST15	10:124007665-124093607	0.2656	0.9527	1.8428	0.0496
ENSG00000222041	LINC00152	2:87439522-87606805	12.0885	26.0682	1.1087	0.0496
ENSG00000180543	TSPYL5	8:97273473-97277964	0.7541	1.6178	1.1013	0.0496
ENSG00000144290	SLC4A10	2:161416093-161985282	1.9943	3.2864	0.7207	0.0496

Supplemental Table 2: Differentially Expressed Genes in T Lymphocytes from 22qDS Patients with Low T cell Counts

Ensembl_id	Gene Symbol	Locus	Normal T cell	Low T cell	log2(FC)	q_value
ENSG00000265185	SNORD3B-1	17:19061911-19062669	6.3369	221.8600	5.1297	0.0135
ENSG00000211942	IGHV3-13	14:106129539-106130072	1.2908	11.6747	3.1771	0.0135
ENSG00000163220	S100A9	1:153357853-153361027	22.0227	100.4070	2.1888	0.0135
ENSG00000277775	HIST1H3F	6:26250194-26250605	21.3749	92.4120	2.1122	0.0135
ENSG00000197249	SERPINA1	14:94376746-94390693	1.7086	7.3367	2.1023	0.0135
ENSG00000273983	HIST1H3G	6:26269404-26271815	3.6708	14.9847	2.0293	0.0135
ENSG00000117399	CDC20	1:43358954-43363203	0.9786	3.9592	2.0164	0.0135
ENSG00000204161	C10orf128	10:49154724-49188585	2.7034	10.8595	2.0061	0.0135
ENSG00000186431	FCAR	19:54874247-54890472	0.1944	0.7673	1.9807	0.0135
ENSG00000143546	S100A8	1:153390031-153391188	8.7548	34.4156	1.9749	0.0135
ENSG00000090382	LYZ	12:69348340-69354234	27.2873	107.1720	1.9736	0.0135
ENSG00000038427	VCAN	5:83471464-83582303	1.4074	5.0988	1.8571	0.0135
ENSG00000211651	IGLV1-44	22:22380765-22381347	12.5019	44.9032	1.8447	0.0135
ENSG00000103313	MEFV	16:3242027-3256627	0.2477	0.8864	1.8392	0.0135
ENSG00000136869	TLR4	9:117704331-117716871	0.4485	1.5510	1.7902	0.0135
ENSG00000146670	CDCA5	11:65066299-65084164	0.7519	2.5602	1.7676	0.0135
ENSG00000211648	IGLV1-47	22:22357738-22358260	9.6157	31.9516	1.7324	0.0135
ENSG00000179639	FCER1A	1:159289713-159308224	3.0226	9.9795	1.7232	0.0135
ENSG00000274997	HIST1H2AH	6:27147128-27147516	24.2778	78.5401	1.6938	0.0135
ENSG00000211955	IGHV3-33	14:106359792-106360324	4.6127	14.5527	1.6576	0.0135
ENSG00000276368	HIST1H2AJ	6:27814353-27814740	9.5851	30.2148	1.6564	0.0135
ENSG00000274267	HIST1H3B	6:26031649-26032060	50.5282	158.0280	1.6450	0.0135
ENSG00000167900	TK1	17:78174074-78187233	1.6661	5.0850	1.6098	0.0135
ENSG00000278196	IGLV2-8	22:22822657-22823293	11.7137	35.4339	1.5969	0.0135
ENSG00000211934	IGHV1-2	14:105986581-105987083	11.9252	34.7485	1.5429	0.0135
ENSG00000273703	HIST1H2BM	6:27815043-27815424	35.9928	103.1120	1.5184	0.0135
ENSG00000007968	E2F2	1:23506429-23531220	1.3061	3.6323	1.4757	0.0135
ENSG00000167513	CDT1	16:88803212-88809258	0.9583	2.6585	1.4721	0.0135
ENSG00000125538	IL1B	2:112829750-112836903	11.2690	31.1052	1.4648	0.0135
ENSG00000018280	SLC11A1	2:218382028-218396894	0.8611	2.3042	1.4200	0.0135
ENSG00000088325	TPX2	20:31739270-31801805	1.4795	3.8304	1.3724	0.0135
ENSG00000171848	RRM2	2:10122327-10131419	3.4742	8.9249	1.3612	0.0135
ENSG00000184357	HIST1H1B	6:27866848-27867529	56.8341	142.1760	1.3229	0.0135
ENSG00000276180	HIST1H4I	6:27138587-27139881	5.7809	14.4135	1.3181	0.0135
ENSG00000275713	HIST1H2BH	6:26251650-26253710	8.4754	20.7245	1.2900	0.0135
ENSG00000196747	HIST1H2AI	6:27808198-27808701	35.3963	84.0203	1.2471	0.0135
ENSG00000274641	HIST1H2BO	6:27893462-27893843	51.6470	116.7910	1.1772	0.0135
ENSG00000124635	HIST1H2BJ	6:27125896-27132750	50.1895	113.2920	1.1746	0.0135
ENSG00000196890	HIST3H2BB	1:228458106-228460470	3.0942	6.8471	1.1459	0.0135
ENSG00000185130	HIST1H2BL	6:27807443-27807931	33.6354	72.8983	1.1159	0.0135
ENSG00000278828	HIST1H3H	6:27810063-27811300	29.1515	62.2407	1.0943	0.0135

Ensembl_id	Gene Symbol	Locus	Normal T cell	Low T cell	log2(FC)	q_value
ENSG00000204287	HLA-DRA	6:32439841-32445046	30.0919	63.1297	1.0689	0.0135
ENSG00000138166	DUSP5	10:110497837-110511544	14.7362	30.7448	1.0610	0.0135
ENSG00000100097	LGALS1	22:37675607-37679806	33.0753	68.7271	1.0551	0.0135
ENSG00000164111	ANXA5	4:121667954-121697113	26.7527	49.9560	0.9010	0.0135
ENSG00000182718	ANXA2	15:60347133-60402883	46.6294	85.1927	0.8695	0.0135
ENSG00000197238	HIST1H4J	6:27824107-27824480	204.1270	372.0370	0.8660	0.0135
ENSG00000196154	S100A4	1:153543612-153550136	176.4910	315.7780	0.8393	0.0135
ENSG00000198355	PIM3	22:49960512-49964080	18.8189	32.2339	0.7764	0.0135
ENSG00000171115	GIMAP8	7:150450629-150479392	22.6812	13.5071	-0.7478	0.0135
ENSG00000201098	RNY1	7:148987135-148987248	23833.8000	14183.9000	-0.7488	0.0135
ENSG00000200156	RNU5B-1	15:65304676-65304792	11555.7000	6454.2800	-0.8403	0.0135
ENSG00000117228	GBP1	1:89052318-89065360	124.0180	53.8582	-1.2033	0.0135
ENSG00000137965	IFI44	1:78649795-78664078	56.0095	23.4551	-1.2558	0.0135
ENSG00000157601	MX1	21:41420303-41459214	108.2700	43.2489	-1.3239	0.0135
ENSG00000184979	USP18	22:18149898-18177397	8.5629	3.3805	-1.3409	0.0135
ENSG00000126709	IFI6	1:27666060-27703063	83.8740	32.9370	-1.3485	0.0135
ENSG00000138642	HERC6	4:88378738-88443111	31.5226	12.2318	-1.3658	0.0135
ENSG00000163520	FBLN2	3:13549130-13638422	3.9023	1.2168	-1.6813	0.0135
ENSG00000137959	IFI44L	1:78619921-78646145	88.7070	22.0840	-2.0061	0.0135
ENSG00000133454	MYO18B	22:25742143-26031041	1.1490	0.1584	-2.8584	0.0135
ENSG00000078081	LAMP3	3:183122212-183163839	12.2068	1.6753	-2.8652	0.0135
ENSG00000215030	RPL13P12	17:17383376-17384012	25.4324	2.1238	-3.5819	0.0135
ENSG00000211892	IGHG4	14:105624340-105626066	110.5270	4.7364	-4.5445	0.0135
ENSG00000171051	FPR1	19:51745171-51826189	0.5425	3.5824	2.7233	0.0233
ENSG00000170458	CD14	5:140631727-140633701	1.0794	3.4870	1.6917	0.0233
ENSG00000197629	MPEG1	11:59171429-59212951	1.4104	3.5464	1.3303	0.0233
ENSG00000186827	TNFRSF4	1:1211325-1214138	4.0507	9.7925	1.2735	0.0233
ENSG00000120875	DUSP4	8:29333063-29350668	6.0067	11.1834	0.8967	0.0233
ENSG00000278771	Metazoa_SRP	14:49853615-49853914	273.1300	487.8760	0.8369	0.0233
ENSG00000135046	ANXA1	9:73151756-73170393	111.6620	187.0740	0.7445	0.0233
ENSG00000171444	MCC	5:113022098-113488830	2.4676	1.1008	-1.1646	0.0233
ENSG00000225840	AC010970.2	Y:10197255-10199103	2.8952	0.6913	-2.0662	0.0233
ENSG00000134321	RSAD2	2:6840569-6898239	23.8634	5.0528	-2.2396	0.0233
ENSG00000243264	IGKV2D-29	2:89947511-89948279	3.4071	11.9661	1.8124	0.0308
ENSG00000101336	HCK	20:32052187-32101856	1.0939	3.0813	1.4941	0.0308
ENSG00000163563	MNDA	1:158831316-158849506	1.8774	5.1187	1.4470	0.0308
ENSG00000124762	CDKN1A	6:36676459-36687339	2.4128	5.4975	1.1881	0.0308
ENSG00000112149	CD83	6:14117255-14136918	5.4988	10.7698	0.9698	0.0308
ENSG00000158050	DUSP2	2:96143165-96145440	92.0621	171.2330	0.8953	0.0308
ENSG00000113088	GZMK	5:54977863-55042844	35.8530	61.4498	0.7773	0.0308
ENSG00000171314	PGAM1	10:97426159-97433441	40.7089	66.1746	0.7009	0.0308
ENSG00000100376	FAM118A	22:45308967-45341955	56.0338	27.2256	-1.0413	0.0308
ENSG00000138646	HERC5	4:88457116-88506163	11.7905	4.9791	-1.2437	0.0308
ENSG00000197705	KLHL14	18:32672670-32774413	0.4217	1.2519	1.5698	0.0375

Ensembl_id	Gene Symbol	Locus	Normal T cell	Low T cell	log2(FC)	q_value
ENSG00000134057	CCNB1	5:69167009-69178245	2.3313	6.0016	1.3642	0.0375
ENSG00000125810	CD93	20:23079348-23086340	0.7979	1.6563	1.0537	0.0375
ENSG00000278463	HIST1H2AB	6:26033175-26033568	30.4666	63.0214	1.0486	0.0375
ENSG00000138160	KIF11	10:92593285-92655395	1.6274	3.1365	0.9466	0.0375
ENSG00000100300	TSPO	22:43151513-43163242	17.3293	32.2891	0.8978	0.0375
ENSG00000132646	PCNA	20:5114952-5126626	22.1986	37.7213	0.7649	0.0375
ENSG00000270103	RNU11	1:28648599-28648733	3969.1000	2255.3200	-0.8155	0.0375
ENSG00000035499	DEPDC1B	5:60596911-60700190	0.5234	1.5898	1.6029	0.0459
ENSG00000028137	TNFRSF1B	1:12166942-12209228	21.2006	33.9466	0.6792	0.0459

Supplemental Table 3: Spearman correlation coefficient (Rho=R) for T cell subsets and genes

Ensembl ID	Gene symbol	CD3 count	CD4 count	CD8 count	Naïve helper count
ENSG00000019582	CD74	-0.82105	-0.8193	-0.7386*	-0.78421
ENSG00000026103	FAS	-0.81053	-0.79649	-0.67193**	-0.80175
ENSG00000073756	PTGS2	-0.83509	-0.79474	-0.74386*	-0.78772
ENSG00000095794	CREM	-0.80526	-0.79474	-0.62105**	-0.83684
ENSG00000107968	MAP3K8	-0.75088*	-0.78947	-0.48772***	-0.84912
ENSG00000113070	HBEGF	-0.77018*	-0.71404*	-0.80175	-0.6807**
ENSG00000113088	GZMK	-0.79825	-0.84737	-0.62982**	-0.87018
ENSG00000115604	IL18R1	-0.84737	-0.83158	-0.74035*	-0.78772
ENSG00000120875	DUSP4	-0.87368	-0.9	-0.68421**	-0.91404
ENSG00000122862	SRGN	-0.82456	-0.84386	-0.70526*	-0.86316
ENSG00000124762	CDKN1A	-0.80877	-0.80351	-0.64561**	-0.89298
ENSG00000130066	SAT1	-0.8	-0.79123	-0.68421**	-0.75439*
ENSG00000131981	LGALS3	-0.84035	-0.82807	-0.69298**	-0.8386
ENSG00000134107	BHLHE40	-0.7614*	-0.80351	-0.57895**	-0.84211
ENSG00000135604	STX11	-0.82456	-0.81228	-0.65965**	-0.8386
ENSG00000137801	THBS1	-0.83684	-0.81053	-0.76316*	-0.83158
ENSG00000138166	DUSP5	-0.81579	-0.80877	-0.70526*	-0.84737
ENSG00000141682	PMAIP1	-0.74561*	-0.80351	-0.50526***	-0.83333
ENSG00000143546	S100A8	-0.71228*	-0.63333**	-0.8	-0.57895**
ENSG00000146192	FGD2	-0.85965	-0.80526	-0.80702	-0.78947
ENSG00000147889	CDKN2A	-0.81754	-0.78246	-0.8	-0.7193*
ENSG00000148175	STOM	-0.73158*	-0.75088*	-0.49825***	-0.8193
ENSG00000163659	TIPARP	-0.7193*	-0.75088*	-0.51228***	-0.84035
ENSG00000172985	SH3RF3	0.81053	0.77368*	0.72982*	0.78246
ENSG00000178573	MAF	-0.79298	-0.81404	-0.67193**	-0.80526
ENSG00000183508	FAM46C	-0.70526*	-0.73158*	-0.52982***	-0.81404
ENSG00000185947	ZNF267	-0.8	-0.79298	-0.72807*	-0.75263*
ENSG00000196126	HLA-DRB1	-0.79298	-0.85965	-0.57895**	-0.86842
ENSG00000271303	SRXN1	-0.83509	-0.88772	-0.60702**	-0.91228

No superscript= p value <0.0001, * =p value<0.001, **=p value<0.01, ***=p value<0.05

Supplemental Table 4: Ensembl Biotypes of 360 Genes

Biotype	Count
Antisense	2
IG_C_gene	11
IG_C_pseudogene	1
IG_V_gene	38
IG_V_pseudogene	1
LincRNA	2
Mt_tRNA	1
Polymorphic_pseudogene	1
Protein_coding	296
Sense_overlapping	1
TEC	2
Transcribed_unprocessed_pseudogene	2

IG, immunoglobulin; C, constant; V, variable; linc, long intergenic noncoding; Mt, mitochondrial; TEC, trans-spliced exon coupled