# Evaluation of Lupus Risk Variants for Their Potential *Cis*-Regulatory Effects on Long Non-coding RNA (LncRNA) Expression

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Submitted to the Graduate Faculty of the

Department of Human Genetics

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2020

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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## Abstract

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease (AID) that results from interactions between environmental and multiple genetic and epigenetic risk factors. Long non-coding RNAs (lncRNAs) are a class of non-protein-coding RNA molecules that execute multiple regulatory functions through their interactions with various (DNA, RNA, protein) molecules. Recent studies increasingly implicate lncRNAs as important regulators of immune response and autoimmunity. A growing body of evidence suggests an important role of non-coding regulatory variants in autoimmunity and recent multi-omics studies also implicate alterations in SNP-lncRNA-mRNA interactions as important contributors to AID onset and pathogenesis. While the aberrant expression of lncRNAs in SLE has recently been reported in multiple studies, only a few studies have proposed or established the potential involvement of GWAS-implicated lncRNAs in SLE. Given that most lncRNAs are relatively novel and only recently mapped to human genome, the SLE risk loci/variants warrant further exploration for their potential *cis*-regulatory effects on both mRNA and lncRNA expression, which is the main purpose of the current study. For this purpose, we performed *in silico* analyses of SLE associated loci/SNPs using the publicly available GTEx Portal (V8) in order to evaluate their *cis*-regulatory effects in SLE-relevant immune cells/tissues (LCLs and spleen). Our analyses have revealed a number of *cis*-regulated lncRNAs

(known or novel) with potential roles in SLE-associated immunopathology, in addition to previously proposed protein-coding genes. Interestingly, the majority of significant SNP–lncRNA associations were observed in the spleen followed by LCLs, and only a small number of lncRNA genes were found to be *cis*-regulated in both spleen and LCLs. Our further *in silico* evaluations using additional bioinformatics tools and databases have revealed that highly SLE-relevant lncRNAs identified in this study were expressed in a wide spectrum of immune cell types (T cells, B cells, NK cells, monocytes), which is also in line with multiple adaptive and innate immune system abnormalities observed in SLE-related immunopathology. In summary, the results of our study provide further support to the recently proposed role of SNP-lncRNA-mRNA networks in immune regulation and autoimmunity. LncRNAs represent exciting pharmaceutical targets due to their ability to interact with a variety of molecules to regulate gene expression. Hence an improved understanding of their roles in SLE may guide future preventive or therapeutic interventions for this chronic autoimmune disease, which represents a significant public health concern due to significant morbidity and mortality.

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# 1.0 Introduction

## 1.1 Immune System and Autoimmunity

Having a properly functioning immune system is a key component to maintaining the physical health of complex organisms. In humans, a competent immune system plays important roles in defending against infections, preventing tumor growth, distinguishing self from non-self (tolerating self antigens), and initiating tissue repair. The immune system is able to accomplish these essential functions through its two distinct, but intertwined types of response: innate and adaptive immunity. While the innate immunity provides the rapid/early response in fight against infection and spread of disease, the adaptive immunity provides a delayed but more specific and stronger response. An innate immune response may include the activation of different cells like granulocytes, monocytes/macrophages, dendritic cells, natural killer (NK) or other innate lymphoid cells, as well as various humoral factors like cytokines and complement system proteins. The components of adaptive immune response include T- and B-cells and the cytokines and antibodies as the major humoral factors(Nicholson, 2016; Parkin & Cohen, 2001).

As with the other human biological systems, there are many diseases and conditions that arise when the immune system fails to function properly. One well-known instance of this is when a person's immune system might fail to distinguish self from non-self and start attacking body's own cells and tissues, resulting in autoimmunity and autoimmune diseases. Various immunologic abnormalities are believed to contribute to the loss of self-tolerance where autoreactive lymphocytes escape the elimination or suppression mechanisms(Nicholson, 2016; Parkin & Cohen, 2001).

## 1.2 Autoimmune Diseases (AIDs)

Autoimmune diseases (AIDs) represent a heterogeneous group of mostly chronic disorders, collectively affecting up to 10% of the general population(Marson, Housley, & Hafler, 2015). We are aware of the existence of over 80 (rare or common) human AIDs (https://www.niaid.nih.gov/diseases-conditions/autoimmune-diseases), which highly vary in clinical manifestation and pathogenesis depending on the triggering autoantigen(s) and targeted self-cells/tissue(s) (Farh et al., 2015). Although the exact molecular mechanisms leading to the development of common AIDs remain largely unknown, abnormalities in both innate and adaptive immune responses appear to be involved in their pathogeneses (L. Wang, Wang, & Gershwin, 2015). As with many other complex (multifactorial) human diseases, common AIDs are believed to result from a combination of, and a complex interplay between, underlying genetic factors and particular environmental influences (Rose, 2016; L. Wang et al., 2015).

Considering their multifactorial nature, studying the genetic aspect may give partial insight into the underlying mechanisms, pathogenesis, and phenotypic heterogeneity of autoimmune diseases. The major histocompatibility complex (MHC) region of the human genome has been associated with many AIDs, which is unsurprising due to the role it plays in antigen presentation(Lessard et al., 2012). Additionally, since the advent of genome-wide association studies (GWAS) hundreds of other loci outside of this MHC region have been associated with at least one autoimmune disease (Lessard et al., 2012; Marson et al., 2015). It should be noted however, that application of data is challenging as many of the AID-associated genes may be differentially expressed among different cell types as well as between populations of different ancestry or geography(Seldin, 2015).

## 1.3 Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is one such chronic disease that results from autoimmunity, characterized by the occurrence of a wide variety of autoantibodies, mainly involving those against nucleoproteins. While the epidemiological data remain limited, incidence and prevalence of SLE are known to differ between ethnic groups within the United States (Stojan & Petri, 2018). African Americans have the highest incidence and prevalence, European Americans have the lowest, and Asian Americans and Hispanics are between the two. Like many other AIDs, SLE shows strong gender bias, affecting more women than men, especially those of reproductive age. The exact mechanisms by which gender-related factors contribute to SLE pathogenesis remain largely unknown but believed to involve sex hormones, sex chromosomal genes, and sex-related differences in epigenetic mechanisms (Chen, Morris, & Vyse, 2017; Di Battista et al., 2018; Mok & Lau, 2003). Despite the ever-growing body of knowledge on SLE and advancements in its management, mortality rates remain about three times higher in SLE patients than in the general population, which warrants greater research efforts into better understanding of this disease in order to guide future prevention, diagnosis, and treatment efforts (Mok & Lau, 2003; Stojan & Petri, 2018).

### 1.3.1 Clinical Features and Management of SLE

SLE is a disease that may manifest as a variety of different clinical signs and symptoms. These manifestations have been noted to involve multiple organs/systems including the skin, joints, hematopoietic, renal, cardiovascular, respiratory, and nervous systems(Di Battista et al., 2018). In the skin, SLE patients have been known to experience Raynaud's phenomenon, irregular

capillary distribution, and to develop malar or discoid rash. The blood of most SLE patients has been shown to be cytopenic. Renal complications of SLE include nephritis, hypertension, and whole organ failure. Different parts of the heart, including the coronary arteries, pericardium, myocardium, and valve tissues, may be affected by SLE(Di Battista et al., 2018). In regards to neurologic features of SLE, patients may develop issues in their central and/or peripheral nervous systems or even psychiatric disorders such as depression(Dias-Santos et al., 2020). Ongoing efforts have been in place to develop and further improve SLE classification criteria in order to bring about uniformity in the definition of SLE for research and surveillance purposes(Hersh et al., 2016), such as American College of Rheumatology (ACR) classification criteria (Aringer, 2019; Hochberg, 1997; Tan et al., 1982) and more recent Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (Petri et al., 2012) for SLE (involving both clinical and laboratory findings). While the mainstream treatment for SLE involves the use of drugs for generalized or targeted immune suppression, the therapy response varies widely among patients, and currently there is no cure for SLE.

### 1.3.2 Immunopathogenesis of SLE

A number of instances of this variable manifestation of disease have been linked to specific biologic pathways; however, a complete understanding of SLE pathogenesis remains out of reach. In regards to the development of autoimmunity, both innate and adaptive immune system abnormalities seem to play important roles in SLE-associated immunopathology, including increased cell death (apoptosis, NETosis) and defective clearance of resulting debris, alterations in antigen processing/presentation and/or immune signaling pathways, T-cell dysfunction, and B-cell hyperfunction (Mok & Lau, 2003; Teruel, Chamberlain, & Alarcon-Riquelme, 2017). Type I

interferons (IFNs) – such as IFN-α cytokine produced by the innate immune system – and related genes/pathways (type I IFN system) are known to play a major role in SLE pathogenesis (Di Battista et al., 2018; Ghodke-Puranik & Niewold, 2015; Kwon, Chun, Kim, & Mak, 2019; Teruel et al., 2017). Another observation in some SLE patients is the defective function of regulatory T cells (Tregs) such as the overproduction of $CD4^{+}CD69^{+}$ Treg cells (Di Battista et al., 2018). Notably, although Tregs are known to have an immunosuppressive effect, the $CD4^{+}CD69^{+}$ T cell subset appears less able to perform this function when found in greater numbers in SLE patients (Vitales-Noyola et al., 2017). SLE manifestations involving the skin have been linked to increased expression of TLR-4, and Chemokine Receptors 1 and 2 (Di Battista et al., 2018). SLE derived lupus nephritis has been associated with several biologic pathways including apoptosis(Di Battista et al., 2018). SLE manifestations in the nervous system have been associated with chronic inflammation. This leads to a decrease in synaptic activity and the death of neurons(Dias-Santos et al., 2020).

### 1.3.3 Genetics of SLE

Considering the heterogeneous nature of SLE, obtaining a comprehensive understanding of the mechanisms of disease has proven to be a challenge. SLE is a multifactorial polygenic disease and genetic information has the potential to provide at least partial insight into the underlying disease mechanisms. Among the SLE-associated loci in the human genome, the major histocompatibility (MHC) locus is known to be the most gene rich and polymorphic, with many of the genes in this locus functioning in the immune system(Chen et al., 2017; Ghodke-Puranik & Niewold, 2015; Kwon et al., 2019; Teruel et al., 2017). That being said, major difficulties are encountered when attempting to identify which specific MHC variants drive SLE pathogenesis

due to extended strong linkage disequilibrium (LD) affecting this large locus. When considering genes lying outside of the MHC locus, variants in more than 80 loci have been linked to SLE susceptibility, mainly implicating single nucleotide polymorphisms (SNPs) with potential regulatory effects on gene expression (Kwon et al., 2019; Teruel et al., 2017). In addition to these changes in the genome, epigenetic effects should also be considered when looking for insights into the mechanisms of such a complex disease as they regulate the gene expression and also interact with environmental factors. One relevant example is that certain T-cells can express greater autoreactivity when their DNA is hypomethylated(Chen et al., 2017; Ghodke-Puranik & Niewold, 2015; Kwon et al., 2019; Teruel et al., 2017). Considering all of this, information surrounding the human genome offers much to be discovered through analysis of its many aspects. One such aspect is the presence of regions of DNA that are transcribed into RNA but do not code for a protein product (Zhao et al., 2018). These non-coding RNAs (ncRNAs) have several subclasses and of these subclasses this study will look with particular interest at the long non-coding class, which is increasingly recognized for important regulatory functions of its members.

### 1.4 Long Non-coding RNAs (LncRNAs)

Long non-coding RNAs (lncRNAs) are a class of transcript of at least 200 bp in size that does not code for a protein but is able to modify expression patterns of specific genes (Ernst & Morton, 2013; Sigdel, Cheng, Wang, Duan, & Zhang, 2015). Within this class of non-coding RNAs, there is still a notable amount of diversity in size, position relative to the target gene(s), processing patterns, and mechanism of action. LncRNAs can range from just a couple hundred bases to several hundred kilobases in size. They can be found within the gene that they regulate,

nearby, between genes, or even on the antisense strand. This class of gene may or may not undergo splicing. While there is a great diversity in these general characteristics of lncRNAs, they do not dictate the function of these transcripts(Ernst & Morton, 2013; Sigdel et al., 2015; Tang, Zhou, Yu, Xue, & Shen, 2017; Zhao et al., 2018).

As for how this class of molecules modifies gene expression, lncRNAs can interact with transcription, post-transcription, post-translation regulators or epigenetic modifiers (**Figure 1** adapted from (Tang et al., 2017)). In terms of epigenetic modifiers, lncRNAs can interact with chromatin modifying proteins or DNA methyl transferases. To modulate gene expression at the transcription level, lncRNAs can function as enhancers or serve as recruitment factors for certain proteins and complexes. LncRNAs are able to modulate post-transcriptional regulation by affecting mRNA stability and associating with the translational machinery. Post-translationally lncRNAs are able to interact with signaling pathway components. This shows that lncRNAs are able to influence the expression and levels of other molecules at any of the stages from pre-transcription to post-translation (Tang et al., 2017; Zhao et al., 2018).

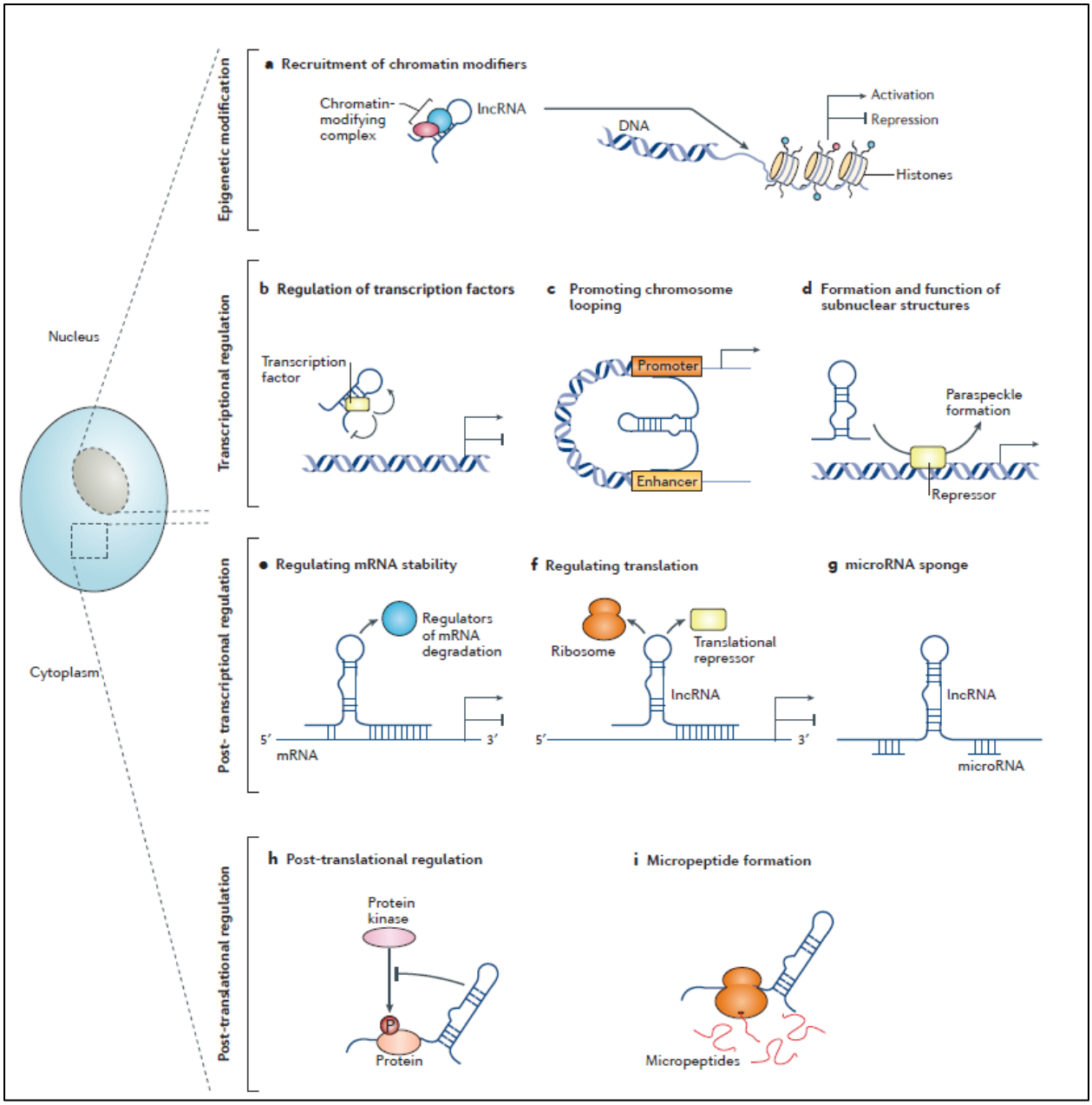



**Figure 1 The functions of long non-coding RNAs in the nucleus and cytoplasm**
Adapted from Tang et al., 2017 (PMID28978995, doi: 10.1038/nrrheum.2017.162)

### 1.4.1 Role of LncRNAs in Immune Regulation and Autoimmunity

LncRNAs have been shown to affect immune genes and in particular play an important role in the development of autoimmunity (Ricano-Ponce et al., 2016; Tang et al., 2017). One study from Aune et al. (2017) has provided a notable amount of insight into this. Their study showed

that many autoimmune diseases had a loss of lncRNA expression with an exception being SLE having a gain of expression, although their SLE sample was small in size. Additionally, they showed that the novel lncRNAs they found were similar to other enhancer-associated lncRNAs. To further expand on this, they showed that certain enhancers were active in certain cell types while others were active across several. This study also was able to show that lncRNAs were located closer to disease-associated SNPs than random chance would explain(Aune et al., 2017). One other study by Ricano-Ponce et al. (2016) found SNPs associated with autoimmune diseases that affect the expression of non-coding RNAs. They also noted that many autoimmune disease associated SNPs affect multiple genes. This study also presents information that indicates that the up or down regulation of certain lncRNAs (e.g. AC104820.2, AP002954.4, RP11-542M13.2) by different AID-associated SNPs may contribute to autoimmunity. Notably, they found that the AP002954.4 lncRNA, which is predominantly expressed in monocytes, can be affected by three distinct SNPs associated with three different AIDs (rheumatoid arthritis, multiple sclerosis, and coeliac disease) (Ricano-Ponce et al., 2016).

### 1.4.2 Role of LncRNAs in SLE

LncRNAs have also been shown to play a role in SLE. Zhao et al. (2018) recorded a number of lncRNAs that may influence SLE pathogenesis in their recent review. NEAT1, up-regulated in SLE, is one such lncRNA as it is able to modulate the expression of certain chemokines, interleukin-6 and -8, as well as activate the type I interferon pathway. A second lncRNA they link to and found down-regulated in SLE is Gas5; a lncRNA that plays an important role in apoptosis and can suppress T-cell proliferation. Lnc-DC is the next that their study indicates as being associated with SLE. Considering how efficacious dendritic cells (DCs) are in the immune system,

it is no surprise that a lncRNA that affects their ability to function is associated with an autoimmune disease like SLE. For some of the lncRNAs, the study results were not as consistent as those clearly indicated for lnc-DC and others mentioned above. Linc0949, which helps to regulate cytokine production, was not shown to be differentially expressed between cases in control in their study. They did find however that linc0949 was lower in cases that had lupus nephritis and overexpressed in cases that did not. The authors mention another study that finds lower levels of linc0949 in SLE patients compared to controls. They go on to explain how drug treatment would have influenced these findings and eventually conclude that linc0949 is downregulated in SLE (Zhao et al., 2018). These and several others showcase the potential lncRNAs possess in obtaining insight into the pathogenic mechanisms of such a complex disease.

While the aberrant expression of lncRNAs has recently been reported in multiple SLE studies and also linked to disease activity or other clinical features (Luo et al., 2018; J. B. Wang et al., 2019; Y. Wang et al., 2018; Wu, Hu, Guan, Ye, & Pan, 2019; Ye et al., 2019; Q. Zhang et al., 2019), the potential involvement of GWAS-implicated lncRNAs in SLE has been proposed or established in only a few studies to date (Demirci et al., 2016; Fan et al., 2020; Zhu et al., 2015).

## 2.0 Study Objective and Aims

While a growing body of evidence predominantly implicates regulatory variants in AIDs (Farh et al., 2015), more recent multi-omics studies (Mo et al., 2019; Mo et al., 2017; Xia et al., 2017) also implicate alterations in complex SNP-lncRNA-mRNA interactions as potential contributors to immune dysregulation and autoimmunity. Given that most lncRNAs are relatively novel, only recently identified with the increased use of total RNAseq methodology, the SLE risk loci/variants remain to be revisited/evaluated for their potential associations with both mRNA and lncRNA expression patterns, which is the main objective of the current study. The study aims are to (i) evaluate SLE risk variants for their potential *cis*-regulatory effects on lncRNA expression at implicated risk loci by performing *in silico* analyses using publicly available databases, (ii) identify a set of highly SLE-relevant lncRNA candidate genes for follow up work on blood samples obtained from patients to directly test the SNP-lncRNA-mRNA interactions in SLE, and (iii) determine the types of immune cells and functions putatively affected by the dysregulation of SLE-relevant lncRNAs by exploring additional public databases and bioinformatics resources.

## 3.0 Methods

The list of SLE-associated SNPs was obtained from http://insidegen.com/insidegen-LUPUS-Associations.html (Chen et al., 2017). The loci with "evidence of association with SLE" included in this list result from studies applying a p-value < 5e-8 in a study population equal to or greater than 1000 people. To create a working dataset to proceed with further investigative measures, relative information (i.e. RefSNP ID, SNP location, risk region, locus gene, risk allele, eGene, and study population(s)) was transferred from the original list to a Microsoft Excel file. For each autosomal SNP on this list (excluding those located at the extended MHC and 8p23inv loci), the genomic location was queried in the Ensembl GRCh37.p13 database and a region +/- 250 kb of the lead SNP in publication (from the most proximal and distal SNPs when >1 SNP was reported for a given locus) was established to define as being nearby to the SNP in question. **Figure 2** provides an example of how these regions were viewed in the browser. All protein-coding (mRNA) and non-coding (ncRNA) genes that fall within or adjacent to this region (except for pseudogenes and small ncRNAs such as miRNAs, snoRNAs, snRNAs, and Y-RNAs) were recorded and cross-referenced with those listed in Genotype-Tissue Expression (GTEx) (Consortium, 2013) V8 Locus Browser to confirm (and update if necessary) the final gene set and IDs to be included in query files (containing SNP ID, Gene ID, and tissue name) prepared for eQTL analysis in the GTEx Portal. The effects of SLE risk variants on the expression of nearby mRNA and lncRNA genes were examined in available immune cells/tissues [Cells_EBV-transformed_lymphocytes (LCLs) and Spleen] using the GTEx Portal's eQTL calculator (V8) (https://www.gtexportal.org/home/testyourown).

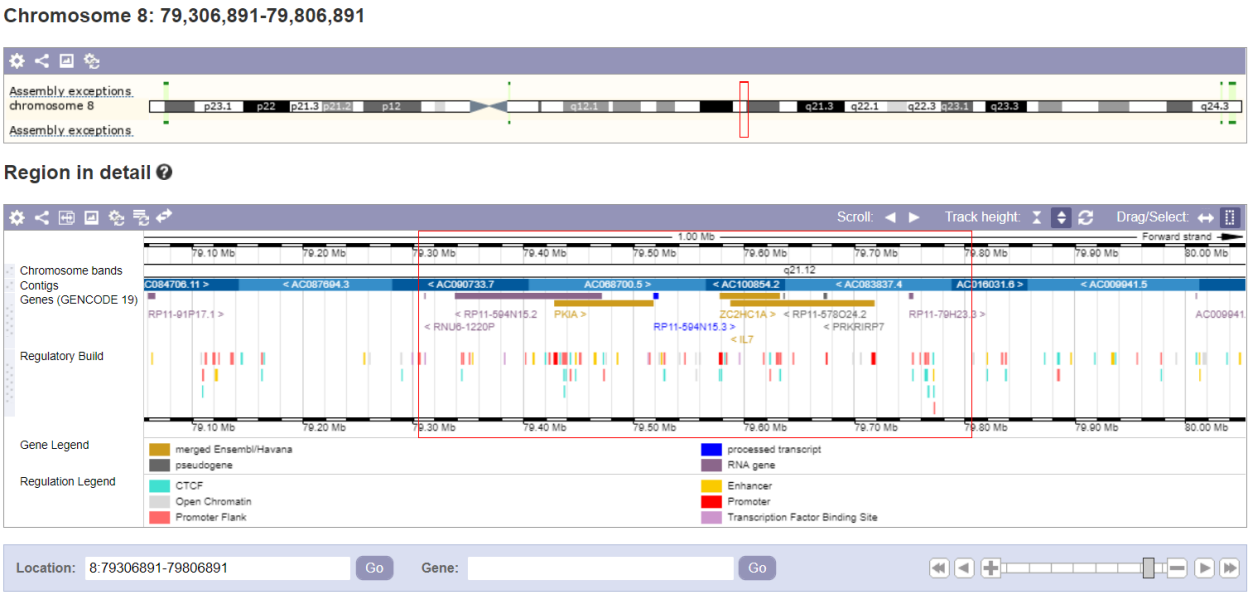



**Figure 2 Ensembl GRCh37.p13 view of the region centered on rs1966115**
The red outlined box represents the +/- 250kb region. Notably, RNA genes are shown in purple, processed transcripts in blue, and coding genes in dark yellow**.**

We also determined the proxy SNPs ($r^2$>=0.8) for each SLE associated SNP using the LDlink suite's LDproxy tool in order to test their potential *cis* eQTL effects in additional immune cells eQTL databases, such as the Database of Immune Cell EQTLs, Expression, Epigenomics (DICE), where the SNP information was limited due to the use of unimputed genotyping data. While the DICE database (Schmiedel et al., 2018) was not very informative for exploring our SNPs of interest, it has provided useful information about the immune cell type-specific expression patters of a subset of highly SLE-relevant lncRNAs identified in this study (see **Results and Discussion**).

## 4.0 Results

Evaluation of more than 130 SNPs (from >75 SLE risk loci) for their potential effects on the expression of *cis* lncRNA genes (within the genomic window described above – see **Methods**) has revealed about 70 significant ($P$<0.05) SNP-lncRNA associations in SLE-relevant immune cells/tissues (LCLs and/or spleen in GTEx V8). These involve more than 40 SLE risk variants and >50 lncRNA genes in total. At these same loci and within the same genomic window examined, the SLE-associated SNPs were found to affect the expression of a larger number of (>135) *cis* protein-coding genes, and in few instances the lncRNA(s) were the only one(s) significantly affected by a given SNP and/or at a given locus. The majority of significant SNP-lncRNA associations were observed in the spleen (>60%) followed by LCLs, and only a small number of lncRNA genes (<10) were found to be *cis*-regulated in both spleen and LCLs.

Here we present a curated list of highly SLE-relevant lncRNA genes, which we consider as strong candidates to be prioritized for our follow-up work on blood samples obtained from patients to directly test and explore the SNP-lncRNA-mRNA interactions in SLE. This curated list was generated by primarily focusing on those loci where at least one SNP-lncRNA association was detected at a significance level of $P$<0.005. The highly significant SNP-lncRNA associations that passed this significance threshold have included 31 SNP-lncRNA pairs (6.0E-36<$P$<4.70E-03), involving 23 lncRNAs and 20 SNPs (from 14 SLE risk loci) (**Table 1**). Of note, 12 of these 14 loci have also shown SNP-mRNA associations that passed the same threshold (**Table 1**). The majority of the highly significant SNP-lncRNA associations were again observed in the spleen (~70%), followed by LCLs, and only a few lncRNAs were found to be *cis*-regulated in both spleen and LCLs by SLE-associated SNPs (**Table 1**). A number of those were also among the top five

lncRNAs (RP11-660L16.2, AP002954.4, DGUOK-AS1, RP11-802O23.3, and RP11-563N6.6) on which the SLE risk variants showed the strongest *cis*-regulatory effect in the entire data set examined in this study, which focused on the *cis* eQTL networks in LCLs and spleen in GTEx V8.

The single-tissue eQTL violin plots extracted from the GTEx eQTL Calculator interface for the highly significant 31 SNP-lncRNA pairs (involving 20 SNPs from 14 loci and 23 lncRNAs) detected in the spleen and/or LCLs are provided in **Figures 3-11**. For the majority of these 14 SLE loci (n=8), the *cis*-regulated lncRNA gene(s) was/were among the top two e-genes detected for SLE-associated SNPs. At nearly half of these loci (n=6), more than one lncRNA gene was among the *cis* e-genes significantly ($P<0.05$) regulated by the SLE-relevant SNPs.

### 4.1 Table and Figures

**Table 1 SLE risk loci where at least one SNP-lncRNA association was detected at a significance level of P<0.005**

| Lead SNP in Original Publication [a] | Variant Id | Gene Symbol [b] | Gencode Id | P-Value [c] | Tissue |
|---|---|---|---|---|---|
| rs1801274 | chr1_161509955_A_G_b38 | RP11-122G18.11 | ENSG00000283317.1 | 2.80E-03 | Spleen |
| rs1801274 | chr1_161509955_A_G_b38 | FCGR2A | ENSG00000143226.13 | 1.30E-02 | Spleen |
| rs1801274 | chr1_161509955_A_G_b38 | SDHC | ENSG00000143252.14 | 1.30E-02 | LCL |
| rs4852324 | chr2_73975451_T_C_b38 | DGUOK-AS1 | ENSG00000237883.1 | 6.60E-07 | LCL |
| rs4852324 | chr2_73975451_T_C_b38 | RP11-287D1.4 | ENSG00000217702.2 | 2.40E-05 | Spleen |
| rs4852324 | chr2_73975451_T_C_b38 | MTHFD2 | ENSG00000065911.11 | 7.30E-04 | LCL |
| rs4852324 | chr2_73975451_T_C_b38 | RP11-287D1.4 | ENSG00000217702.2 | 6.50E-03 | LCL |
| rs4852324 | chr2_73975451_T_C_b38 | TPRKB | ENSG00000144034.14 | 1.60E-02 | Spleen |
| rs4852324 | chr2_73975451_T_C_b38 | DGUOK-AS1 | ENSG00000237883.1 | 2.40E-02 | Spleen |
| rs4852324 | chr2_73975451_T_C_b38 | MOB1A | ENSG00000114978.17 | 2.70E-02 | LCL |
| rs4852324 | chr2_73975451_T_C_b38 | SLC4A5 | ENSG00000188687.17 | 4.10E-02 | Spleen |
| rs6705628 | chr2_73981235_C_T_b38 | DGUOK | ENSG00000114956.19 | 4.50E-03 | LCL |
| rs6705628 | chr2_73981235_C_T_b38 | TET3 | ENSG00000187605.15 | 4.20E-02 | Spleen |
| rs6445972 | chr3_58335980_C_T_b38 | PXK | ENSG00000168297.15 | 1.10E-07 | Spleen |
| rs6445972 | chr3_58335980_C_T_b38 | RPP14 | ENSG00000163684.11 | 2.10E-07 | Spleen |
| rs6445972 | chr3_58335980_C_T_b38 | ABHD6 | ENSG00000163686.14 | 4.90E-06 | Spleen |
| rs6445972 | chr3_58335980_C_T_b38 | RP11-802O23.3 | ENSG00000272182.1 | 6.10E-06 | Spleen |
| rs6445972 | chr3_58335980_C_T_b38 | RP11-802O23.3 | ENSG00000272182.1 | 1.40E-03 | LCL |
| rs6445972 | chr3_58335980_C_T_b38 | PXK | ENSG00000168297.15 | 7.00E-03 | LCL |
| rs6445972 | chr3_58335980_C_T_b38 | FAM107A | ENSG00000168309.16 | 1.50E-02 | LCL |
| rs6445972 | chr3_58335980_C_T_b38 | ABHD6 | ENSG00000163686.14 | 3.30E-02 | LCL |
| rs6445975 | chr3_58384450_G_T_b38 | PXK | ENSG00000168297.15 | 6.00E-14 | Spleen |
| rs6445975 | chr3_58384450_G_T_b38 | PDHB | ENSG00000168291.12 | 8.00E-07 | Spleen |
| rs6445975 | chr3_58384450_G_T_b38 | FLNB-AS1 | ENSG00000244161.1 | 2.90E-03 | Spleen |
| rs6445975 | chr3_58384450_G_T_b38 | PXK | ENSG00000168297.15 | 5.90E-03 | LCL |
| rs6445975 | chr3_58384450_G_T_b38 | ABHD6 | ENSG00000163686.14 | 1.20E-02 | Spleen |
| rs9311676 | chr3_58484624_C_T_b38 | PXK | ENSG00000168297.15 | 3.20E-06 | Spleen |
| rs9311676 | chr3_58484624_C_T_b38 | RP11-802O23.3 | ENSG00000272182.1 | 6.40E-05 | Spleen |
| rs9311676 | chr3_58484624_C_T_b38 | ABHD6 | ENSG00000163686.14 | 2.60E-04 | Spleen |
| rs9311676 | chr3_58484624_C_T_b38 | RP11-802O23.3 | ENSG00000272182.1 | 6.70E-04 | LCL |
| rs9311676 | chr3_58484624_C_T_b38 | RPP14 | ENSG00000163684.11 | 2.70E-03 | Spleen |
| rs9311676 | chr3_58484624_C_T_b38 | FLNB-AS1 | ENSG00000244161.1 | 1.20E-02 | Spleen |
| rs9311676 | chr3_58484624_C_T_b38 | FAM107A | ENSG00000168309.16 | 2.70E-02 | LCL |
| rs1966115 | chr8_78644656_A_G_b38 | ZC2HC1A | ENSG00000104427.11 | 1.50E-21 | LCL |
| rs1966115 | chr8_78644656_A_G_b38 | PKIA | ENSG00000171033.12 | 4.30E-06 | LCL |
| rs1966115 | chr8_78644656_A_G_b38 | ZC2HC1A | ENSG00000104427.11 | 3.10E-05 | Spleen |
| rs1966115 | chr8_78644656_A_G_b38 | RP11-79H23.3 | ENSG00000261618.1 | 4.70E-03 | LCL |
| rs1966115 | chr8_78644656_A_G_b38 | IL7 | ENSG00000104432.13 | 1.00E-02 | Spleen |
| rs1966115 | chr8_78644656_A_G_b38 | IL7 | ENSG00000104432.13 | 2.30E-02 | LCL |

**Table 1 Continued**

| | | | | | |
|---|---|---|---|---|---|
| rs1966115 | chr8_78644656_A_G_b38 | PKIA | ENSG00000171033.12 | 2.40E-02 | Spleen |
| rs7097397 | chr10_48817351_G_A_b38 | RP11-563N6.6 | ENSG00000228403.1 | 2.00E-05 | Spleen |
| rs7097397 | chr10_48817351_G_A_b38 | RP11-563N6.6 | ENSG00000228403.1 | 7.10E-03 | LCL |
| rs877819 | chr10_48834906_A_G_b38 | WDFY4 | ENSG00000128815.19 | 2.10E-04 | Spleen |
| rs877819 | chr10_48834906_A_G_b38 | WDFY4 | ENSG00000128815.19 | 2.60E-02 | LCL |
| rs4917385 | chr10_103243964_T_G_b38 | USMG5 | ENSG00000173915.14 | 3.90E-06 | LCL |
| rs4917385 | chr10_103243964_T_G_b38 | RP11-724N1.1 | ENSG00000272912.1 | 6.80E-04 | Spleen |
| rs4917385 | chr10_103243964_T_G_b38 | BORCS7 | ENSG00000166275.15 | 1.20E-03 | LCL |
| rs4917385 | chr10_103243964_T_G_b38 | NT5C2 | ENSG00000076685.18 | 3.70E-03 | Spleen |
| rs4917385 | chr10_103243964_T_G_b38 | INA | ENSG00000148798.10 | 5.50E-03 | LCL |
| rs4917385 | chr10_103243964_T_G_b38 | BORCS7 | ENSG00000166275.15 | 2.50E-02 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | MAP3K11 | ENSG00000173327.7 | 1.70E-05 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | SNX32 | ENSG00000172803.17 | 8.70E-05 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | CTSW | ENSG00000172543.7 | 2.30E-03 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | OVOL1 | ENSG00000172818.9 | 2.80E-03 | LCL |
| rs2009453 | chr11_65632057_C_T_b38 | BANF1 | ENSG00000175334.7 | 3.00E-03 | LCL |
| rs2009453 | chr11_65632057_C_T_b38 | NEAT1 | ENSG00000245532.7 | 3.20E-03 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | NEAT1 | ENSG00000245532.7 | 4.40E-03 | LCL |
| rs2009453 | chr11_65632057_C_T_b38 | PCNX3 | ENSG00000197136.4 | 7.00E-03 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | SLC25A45 | ENSG00000162241.12 | 1.10E-02 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | FIBP | ENSG00000172500.12 | 1.20E-02 | LCL |
| rs2009453 | chr11_65632057_C_T_b38 | FAM89B | ENSG00000176973.7 | 1.50E-02 | LCL |
| rs2009453 | chr11_65632057_C_T_b38 | EIF1AD | ENSG00000175376.8 | 2.10E-02 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | RNASEH2C | ENSG00000172922.8 | 2.20E-02 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | SIPA1 | ENSG00000213445.9 | 4.00E-02 | LCL |
| rs2009453 | chr11_65632057_C_T_b38 | AP5B1 | ENSG00000254470.2 | 4.10E-02 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | CCDC85B | ENSG00000175602.3 | 4.20E-02 | Spleen |
| rs2009453 | chr11_65632057_C_T_b38 | RNASEH2C | ENSG00000172922.8 | 4.70E-02 | LCL |
| rs2009453 | chr11_65632057_C_T_b38 | OVOL1 | ENSG00000172818.9 | 4.90E-02 | Spleen |
| rs1308020 | chr11_65730087_G_A_b38 | MAP3K11 | ENSG00000173327.7 | 1.80E-11 | Spleen |
| rs1308020 | chr11_65730087_G_A_b38 | OVOL1-AS1 | ENSG00000255120.5 | 2.10E-04 | Spleen |
| rs1308020 | chr11_65730087_G_A_b38 | NEAT1 | ENSG00000245532.7 | 1.10E-03 | Spleen |
| rs1308020 | chr11_65730087_G_A_b38 | FIBP | ENSG00000172500.12 | 1.60E-03 | Spleen |
| rs1308020 | chr11_65730087_G_A_b38 | LTBP3 | ENSG00000168056.15 | 2.30E-03 | LCL |
| rs1308020 | chr11_65730087_G_A_b38 | RP11-770G2.2 | ENSG00000255557.1 | 2.90E-03 | Spleen |
| rs1308020 | chr11_65730087_G_A_b38 | SIPA1 | ENSG00000213445.9 | 3.90E-03 | LCL |
| rs1308020 | chr11_65730087_G_A_b38 | FIBP | ENSG00000172500.12 | 3.90E-03 | LCL |
| rs1308020 | chr11_65730087_G_A_b38 | MAP3K11 | ENSG00000173327.7 | 4.40E-03 | LCL |
| rs1308020 | chr11_65730087_G_A_b38 | PCNX3 | ENSG00000197136.4 | 1.70E-02 | Spleen |
| rs1308020 | chr11_65730087_G_A_b38 | SNX32 | ENSG00000172803.17 | 1.80E-02 | LCL |
| rs1308020 | chr11_65730087_G_A_b38 | SSSCA1-AS1 | ENSG00000260233.3 | 2.10E-02 | Spleen |
| rs1308020 | chr11_65730087_G_A_b38 | KAT5 | ENSG00000172977.12 | 3.10E-02 | Spleen |
| rs1308020 | chr11_65730087_G_A_b38 | MUS81 | ENSG00000172732.11 | 3.30E-02 | Spleen |
| rs494003 | chr11_65774827_G_A_b38 | SNX32 | ENSG00000172803.17 | 8.90E-07 | Spleen |

**Table 1 Continued**

| | | | | | |
|---|---|---|---|---|---|
| rs494003 | chr11_65774827_G_A_b38 | RNASEH2C | ENSG00000172922.8 | 1.90E-05 | Spleen |
| rs494003 | chr11_65774827_G_A_b38 | OVOL1 | ENSG00000172818.9 | 6.70E-05 | LCL |
| rs494003 | chr11_65774827_G_A_b38 | AP5B1 | ENSG00000254470.2 | 2.20E-04 | LCL |
| rs494003 | chr11_65774827_G_A_b38 | FIBP | ENSG00000172500.12 | 5.40E-04 | LCL |
| rs494003 | chr11_65774827_G_A_b38 | CTSW | ENSG00000172543.7 | 1.70E-03 | Spleen |
| rs494003 | chr11_65774827_G_A_b38 | OVOL1 | ENSG00000172818.9 | 6.30E-03 | Spleen |
| rs494003 | chr11_65774827_G_A_b38 | MAP3K11 | ENSG00000173327.7 | 6.60E-03 | Spleen |
| rs494003 | chr11_65774827_G_A_b38 | SNX32 | ENSG00000172803.17 | 2.20E-02 | LCL |
| rs494003 | chr11_65774827_G_A_b38 | KCNK7 | ENSG00000173338.12 | 2.30E-02 | LCL |
| rs494003 | chr11_65774827_G_A_b38 | FIBP | ENSG00000172500.12 | 2.30E-02 | Spleen |
| rs494003 | chr11_65774827_G_A_b38 | KAT5 | ENSG00000172977.12 | 3.20E-02 | LCL |
| rs494003 | chr11_65774827_G_A_b38 | LTBP3 | ENSG00000168056.15 | 3.20E-02 | Spleen |
| rs3794060 | chr11_71476633_C_T_b38 | RP11-660L16.2 | ENSG00000254682.1 | 6.00E-36 | Spleen |
| rs3794060 | chr11_71476633_C_T_b38 | NADSYN1 | ENSG00000172890.11 | 1.30E-22 | Spleen |
| rs3794060 | chr11_71476633_C_T_b38 | RP11-660L16.2 | ENSG00000254682.1 | 1.30E-21 | LCL |
| rs3794060 | chr11_71476633_C_T_b38 | NADSYN1 | ENSG00000172890.11 | 2.10E-10 | LCL |
| rs3794060 | chr11_71476633_C_T_b38 | KRTAP5-9 | ENSG00000254997.3 | 2.40E-02 | Spleen |
| rs3794060 | chr11_71476633_C_T_b38 | KRTAP5-9 | ENSG00000254997.3 | 3.10E-02 | LCL |
| rs11603023 | chr11_118615352_T_C_b38 | AP002954.4 | ENSG00000255422.1 | 7.50E-08 | Spleen |
| rs11603023 | chr11_118615352_T_C_b38 | PHLDB1 | ENSG00000019144.18 | 2.70E-05 | Spleen |
| rs11603023 | chr11_118615352_T_C_b38 | RP11-158I9.8 | ENSG00000278376.1 | 1.70E-04 | Spleen |
| rs11603023 | chr11_118615352_T_C_b38 | DDX6 | ENSG00000110367.11 | 1.90E-03 | Spleen |
| rs11603023 | chr11_118615352_T_C_b38 | C2CD2L | ENSG00000172375.12 | 8.50E-03 | Spleen |
| rs11603023 | chr11_118615352_T_C_b38 | VPS11 | ENSG00000160695.14 | 1.40E-02 | LCL |
| rs11603023 | chr11_118615352_T_C_b38 | TTC36 | ENSG00000172425.10 | 2.50E-02 | Spleen |
| rs4639966 | chr11_118702810_T_C_b38 | DDX6 | ENSG00000110367.11 | 7.80E-09 | Spleen |
| rs4639966 | chr11_118702810_T_C_b38 | AP002954.4 | ENSG00000255422.1 | 6.10E-05 | Spleen |
| rs4639966 | chr11_118702810_T_C_b38 | PHLDB1 | ENSG00000019144.18 | 1.40E-02 | LCL |
| rs4639966 | chr11_118702810_T_C_b38 | RPS25 | ENSG00000118181.10 | 1.90E-02 | Spleen |
| rs4639966 | chr11_118702810_T_C_b38 | PHLDB1 | ENSG00000019144.18 | 1.90E-02 | Spleen |
| rs4639966 | chr11_118702810_T_C_b38 | SLC37A4 | ENSG00000137700.17 | 2.30E-02 | LCL |
| rs4639966 | chr11_118702810_T_C_b38 | IFT46 | ENSG00000118096.7 | 2.90E-02 | LCL |
| rs4639966 | chr11_118702810_T_C_b38 | ARCN1 | ENSG00000095139.13 | 3.00E-02 | Spleen |
| rs10892301 | chr11_118864767_G_A_b38 | DDX6 | ENSG00000110367.11 | 3.40E-04 | Spleen |
| rs10892301 | chr11_118864767_G_A_b38 | RP11-158I9.8 | ENSG00000278376.1 | 3.80E-04 | Spleen |
| rs10892301 | chr11_118864767_G_A_b38 | VPS11 | ENSG00000160695.14 | 3.20E-03 | LCL |
| rs10892301 | chr11_118864767_G_A_b38 | C2CD2L | ENSG00000172375.12 | 8.80E-03 | Spleen |
| rs10892301 | chr11_118864767_G_A_b38 | TTC36 | ENSG00000172425.10 | 1.30E-02 | Spleen |
| rs10892301 | chr11_118864767_G_A_b38 | AP002954.4 | ENSG00000255422.1 | 2.30E-02 | Spleen |
| rs10892301 | chr11_118864767_G_A_b38 | PHLDB1 | ENSG00000019144.18 | 2.70E-02 | Spleen |
| rs10892301 | chr11_118864767_G_A_b38 | UPK2 | ENSG00000110375.2 | 4.00E-02 | Spleen |
| rs10892301 | chr11_118864767_G_A_b38 | RP11-770J1.5 | ENSG00000254873.1 | 4.80E-02 | LCL |
| rs10774625 | chr12_111472415_A_G_b38 | RP3-473L9.4 | ENSG00000257595.2 | 1.90E-04 | Spleen |
| rs10774625 | chr12_111472415_A_G_b38 | FAM109A | ENSG00000198324.13 | 5.70E-03 | Spleen |

**Table 1 Continued**

| | | | | | |
|---|---|---|---|---|---|
| rs10774625 | chr12_111472415_A_G_b38 | ATXN2-AS | ENSG00000258099.1 | 7.70E-03 | Spleen |
| rs10774625 | chr12_111472415_A_G_b38 | SH2B3 | ENSG00000111252.10 | 4.60E-02 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | KAT8 | ENSG00000103510.19 | 1.00E-04 | LCL |
| rs7197475 | chr16_30631546_C_T_b38 | RP11-196G11.2 | ENSG00000260911.2 | 6.40E-04 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | RP11-388M20.6 | ENSG00000260304.1 | 1.70E-03 | LCL |
| rs7197475 | chr16_30631546_C_T_b38 | RP11-452L6.5 | ENSG00000260267.1 | 3.60E-03 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | RP11-452L6.7 | ENSG00000260625.2 | 1.30E-02 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | HSD3B7 | ENSG00000099377.13 | 1.30E-02 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | PRR14 | ENSG00000156858.11 | 1.40E-02 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | STX4 | ENSG00000103496.14 | 1.60E-02 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | CTF1 | ENSG00000150281.6 | 2.30E-02 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | AHSP | ENSG00000169877.9 | 2.50E-02 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | KAT8 | ENSG00000103510.19 | 2.60E-02 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | ZNF668 | ENSG00000167394.12 | 2.70E-02 | Spleen |
| rs7197475 | chr16_30631546_C_T_b38 | SEPHS2 | ENSG00000179918.18 | 4.90E-02 | LCL |
| rs34572943 | chr16_31261032_G_A_b38 | RP11-347C12.10 | ENSG00000260219.2 | 9.10E-04 | LCL |
| rs34572943 | chr16_31261032_G_A_b38 | RP11-196G11.6 | ENSG00000232748.3 | 4.40E-03 | LCL |
| rs34572943 | chr16_31261032_G_A_b38 | ZNF668 | ENSG00000167394.12 | 1.10E-02 | LCL |
| rs34572943 | chr16_31261032_G_A_b38 | FBXL19-AS1 | ENSG00000260852.1 | 1.20E-02 | LCL |
| rs34572943 | chr16_31261032_G_A_b38 | AHSP | ENSG00000169877.9 | 1.60E-02 | Spleen |
| rs34572943 | chr16_31261032_G_A_b38 | FBXL19-AS1 | ENSG00000260852.1 | 1.80E-02 | Spleen |
| rs34572943 | chr16_31261032_G_A_b38 | STX1B | ENSG00000099365.10 | 2.40E-02 | LCL |
| rs11574637 | chr16_31357553_T_C_b38 | BCL7C | ENSG00000099385.11 | 8.10E-03 | Spleen |
| rs11574637 | chr16_31357553_T_C_b38 | CTF1 | ENSG00000150281.6 | 1.00E-02 | LCL |
| rs11574637 | chr16_31357553_T_C_b38 | RP11-146F11.1 | ENSG00000261840.2 | 4.00E-02 | Spleen |
| rs11574637 | chr16_31357553_T_C_b38 | RP11-347C12.10 | ENSG00000260219.2 | 4.40E-02 | LCL |
| rs1170426 | chr16_68569895_C_T_b38 | ZFP90 | ENSG00000184939.15 | 2.60E-35 | Spleen |
| rs1170426 | chr16_68569895_C_T_b38 | ZFP90 | ENSG00000184939.15 | 6.90E-08 | LCL |
| rs1170426 | chr16_68569895_C_T_b38 | CDH1 | ENSG00000039068.18 | 7.00E-05 | Spleen |
| rs1170426 | chr16_68569895_C_T_b38 | RP11-615I2.6 | ENSG00000275383.1 | 1.40E-03 | Spleen |
| rs1170426 | chr16_68569895_C_T_b38 | CDH1 | ENSG00000039068.18 | 4.40E-03 | LCL |
| rs1170426 | chr16_68569895_C_T_b38 | PRMT7 | ENSG00000132600.16 | 1.80E-02 | LCL |
| rs2941509 | chr17_39764941_T_C_b38 | ERBB2 | ENSG00000141736.13 | 2.70E-04 | LCL |
| rs2941509 | chr17_39764941_T_C_b38 | GSDMB | ENSG00000073605.18 | 5.60E-04 | LCL |
| rs2941509 | chr17_39764941_T_C_b38 | PGAP3 | ENSG00000161395.13 | 1.90E-03 | LCL |
| rs2941509 | chr17_39764941_T_C_b38 | RP11-387H17.6 | ENSG00000265799.1 | 3.70E-03 | Spleen |
| rs2941509 | chr17_39764941_T_C_b38 | NEUROD2 | ENSG00000171532.4 | 5.30E-03 | LCL |
| rs2941509 | chr17_39764941_T_C_b38 | ORMDL3 | ENSG00000172057.9 | 6.00E-03 | LCL |
| rs2941509 | chr17_39764941_T_C_b38 | CSF3 | ENSG00000108342.12 | 8.60E-03 | Spleen |
| rs2941509 | chr17_39764941_T_C_b38 | MED24 | ENSG00000008838.19 | 2.40E-02 | Spleen |
| rs2941509 | chr17_39764941_T_C_b38 | STARD3 | ENSG00000131748.15 | 4.00E-02 | Spleen |
| rs463426 | chr22_21454896_T_C_b38 | CCDC116 | ENSG00000161180.10 | 1.60E-04 | Spleen |
| rs463426 | chr22_21454896_T_C_b38 | SDF2L1 | ENSG00000128228.4 | 7.80E-03 | LCL |
| rs463426 | chr22_21454896_T_C_b38 | YPEL1 | ENSG00000100027.14 | 1.50E-02 | Spleen |

**Table 1 Continued**

| | | | | | |
|---|---|---|---|---|---|
| rs463426 | chr22_21454896_T_C_b38 | MAPK1 | ENSG00000100030.14 | 4.20E-02 | LCL |
| rs131654 | chr22_21562901_G_T_b38 | PI4KAP2 | ENSG00000183506.17 | 2.00E-03 | Spleen |
| rs7444 | chr22_21622645_T_C_b38 | CCDC116 | ENSG00000161180.10 | 1.50E-11 | Spleen |
| rs7444 | chr22_21622645_T_C_b38 | UBE2L3 | ENSG00000185651.14 | 6.50E-05 | Spleen |
| rs7444 | chr22_21622645_T_C_b38 | KB-1440D3.14 | ENSG00000273342.1 | 7.00E-04 | Spleen |
| rs7444 | chr22_21622645_T_C_b38 | PPIL2 | ENSG00000100023.18 | 1.20E-03 | Spleen |
| rs7444 | chr22_21622645_T_C_b38 | YPEL1 | ENSG00000100027.14 | 2.30E-03 | Spleen |
| rs7444 | chr22_21622645_T_C_b38 | MAPK1 | ENSG00000100030.14 | 3.60E-02 | Spleen |
| rs7444 | chr22_21622645_T_C_b38 | SDF2L1 | ENSG00000128228.4 | 4.20E-02 | LCL |

Associations noted in gray text are SNPs that are only associated with expression changes of coding genes. Horizontal lines separate different loci. a) The original paper's table can be found at http://insidegen.com/insidegen-LUPUS-Associations.html. b) Gene symbol names noted in red/orange are lncRNAs and those noted in orange are antisense lncRNAs. c) Highlighted *P*-values are those that pass the high significance threshold ($P<0.005$) that we set to identify/select a set of most SLE-relevant lncRNAs to be examined in follow-up studies.

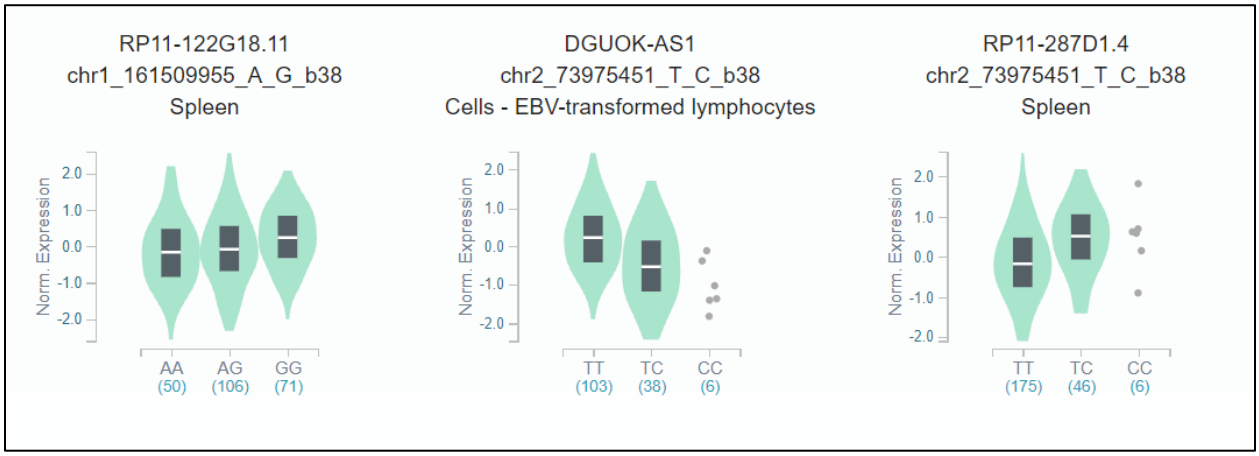



**Figure 3 GTEx eQTL violin plots for highly significant (*P*<0.005) lncRNA expression changes associated with rs1801274 (left) and rs4852324 (right2)**
Plots were extracted from GTEx V8 eQTL calculator tool. In the original paper (Chen et al., 2017) the SLE risk alleles reported for these SNPs are: rs1801274 – C, rs4852324 – T.

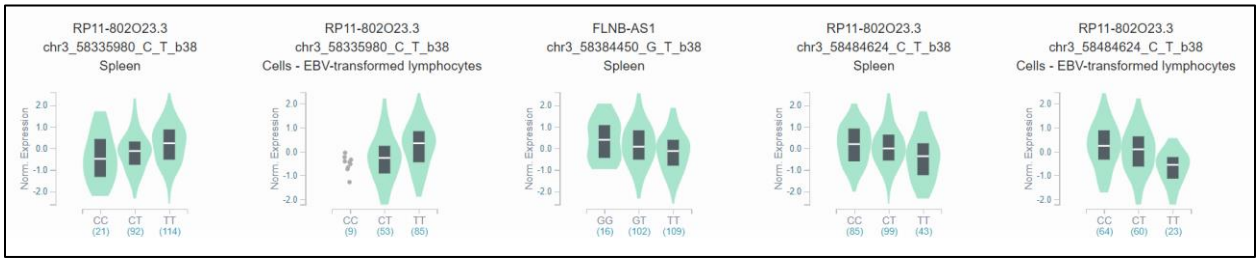



**Figure 4 GTEx eQTL violin plots for highly significant (*P*<0.005) lncRNA expression changes associated with rs6445972 (left2), rs6445975 (center), and rs9311676 (right2)**
Plots were extracted from GTEx V8 eQTL calculator tool. In the original paper (Chen et al., 2017) the SLE risk alleles reported for these SNPs are: rs6445972 – C, rs6445975 – C, rs9311676 – C**.**

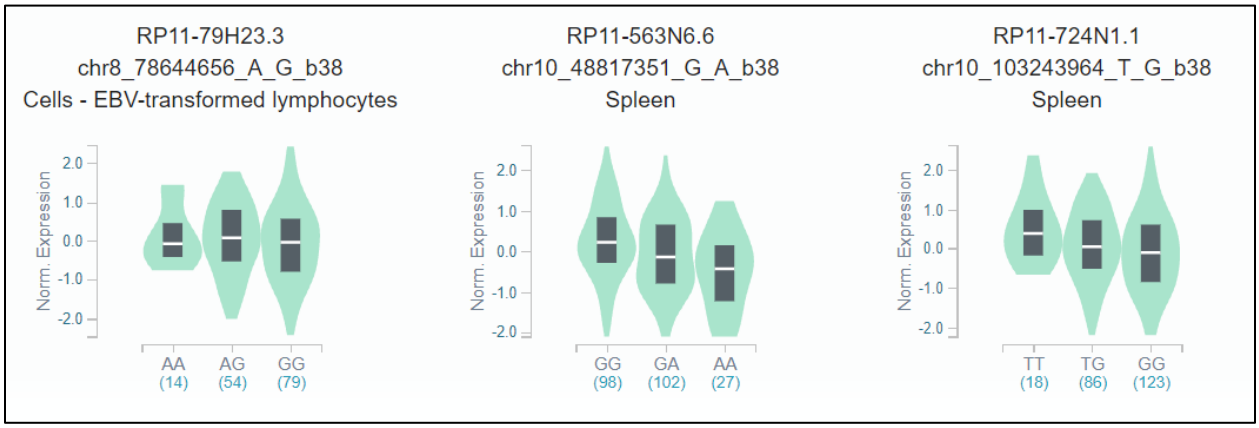



**Figure 5 GTEx eQTL violin plots for highly significant (*P*<0.005) lncRNA expression changes associated with rs1966115 (left), rs7097397 (center), and rs4917385 (right)**

Plots were extracted from GTEx V8 eQTL calculator tool. In the original paper (Chen et al., 2017) the SLE risk alleles reported for these SNPs are: rs1966115 – A, rs7097397 – G, rs4917385 – NA**.**

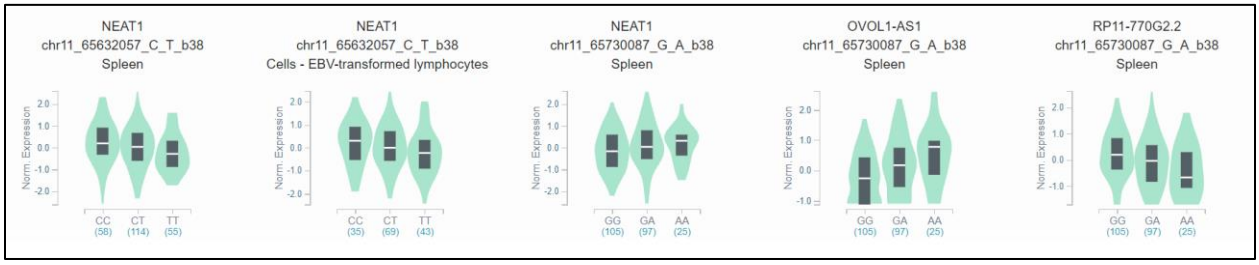



**Figure 6 GTEx eQTL violin plots for highly significant (*P*<0.005) lncRNA expression changes associated with rs2009453 (left2), rs1308020 (right3).**

Plots were extracted from GTEx V8 eQTL calculator tool. In the original paper (Chen et al., 2017) the SLE risk alleles reported for these SNPs are: rs2009453 – C, rs1308020 – T.

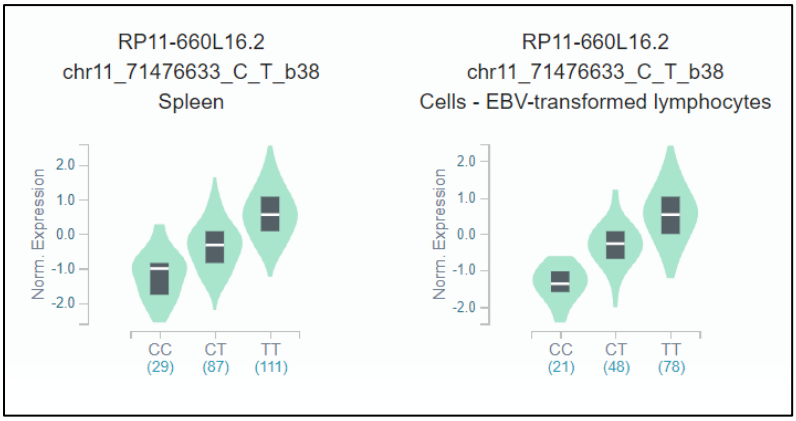



**Figure 7 GTEx eQTL violin plots for highly significant (*P*<0.005) lncRNA expression changes associated with rs3794060.**

Plots were extracted from GTEx V8 eQTL calculator tool. In the original paper (Chen et al., 2017) the SLE risk allele reported for this SNP is: rs3794060 – C.

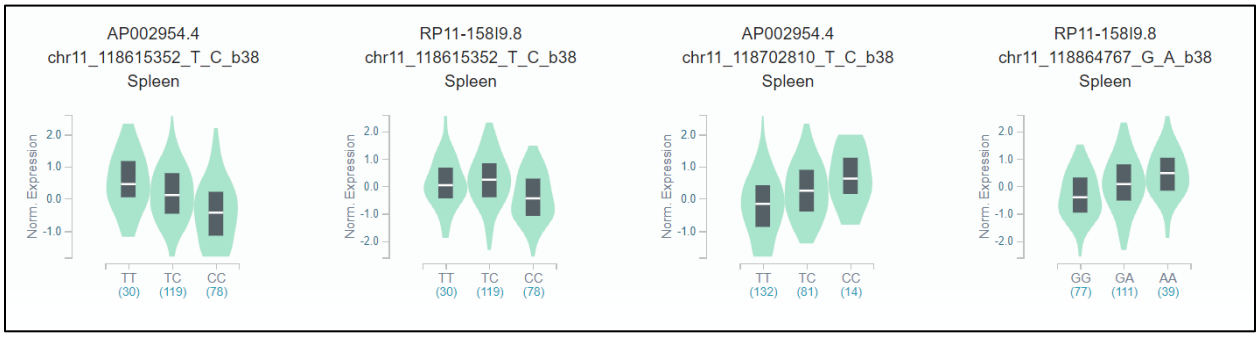



**Figure 8 GTEx eQTL violin plots for highly significant (*P*<0.005) lncRNA expression changes associated with rs11603023 (left2), rs4639966 (right), and rs10892301 (far right)**

Plots were extracted from GTEx V8 eQTL calculator tool. In the original paper (Chen et al., 2017) the SLE risk alleles reported for these SNPs are: rs11603023 – T, rs4639966 – G, rs10892301 – G.

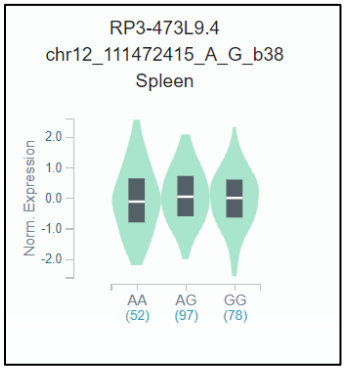



**Figure 9 GTEx eQTL violin plot for highly significant (*P*<0.005) lncRNA expression change associated with rs10774625**

Plot was extracted from GTEx V8 eQTL calculator tool. In the original paper (Chen et al., 2017) the SLE risk allele reported for this SNPs is: rs10774625 – A.

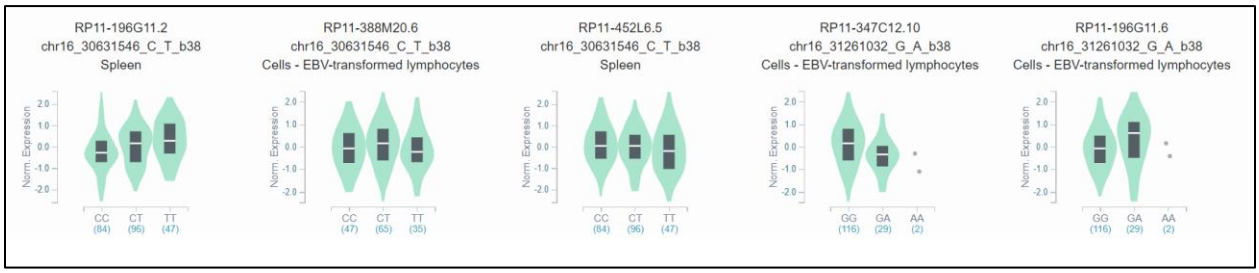



**Figure 10 GTEx eQTL violin plots for highly significant (*P*<0.005) lncRNA expression changes associated with rs7197475 (left3) and rs34572943 (right2).**

Plots were extracted from GTEx V8 eQTL calculator tool. In the original paper (Chen et al., 2017) the SLE risk alleles reported for these SNPs are: rs7197475 – A, rs34572943 – A.

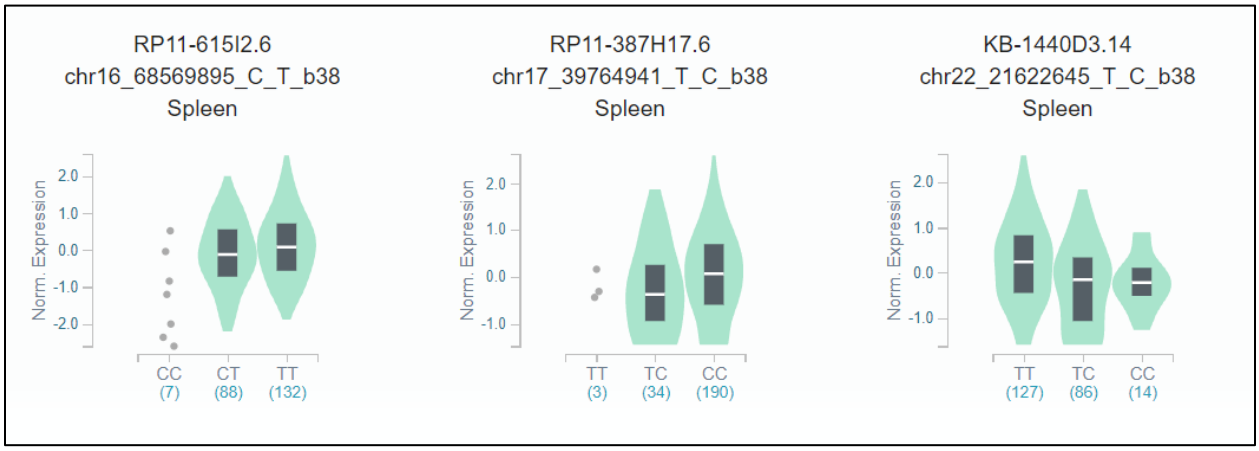



**Figure 11 GTEx eQTL violin plots for highly significant (*P*<0.005) lncRNA expression changes associated with rs1170426 (left), rs2941509 (center), and rs7444 (right)**

Plots were extracted from GTEx V8 eQTL calculator tool. In the original paper (Chen et al., 2017) the SLE risk alleles reported for these SNPs are: rs1170426 – C, rs2941509 – A, rs7444 – C.

## 5.0 Discussion

SLE is a notably heterogenous disease where insights into its causative mechanisms are lacking. As a chronic AID predominantly targeting relatively young women, and with no available cure, SLE continues to pose significant health and economic burden on the society and remains as a significant public health concern.

SLE is a genetically complex disease with >80 risk loci/variants discovered by GWASs(Chen et al., 2017); however, the functional consequences of these SLE risk variants [causative gene(s) and biological mechanisms] remain to be identified for most of these GWAS-identified loci. Majority of SLE-associated SNPs reside outside of the protein-coding genome and are believed to affect the regulatory elements that mediate gene expression(Farh et al., 2015). Although the initial eQTL studies mostly focused on the associations between the disease risk variants and expression of protein-coding genes (mRNAs), advances in NGS technologies and accumulating data from RNA-seq studies have increasingly showed that a large portion of the human genome is transcribed into non-coding transcripts of different sizes (ncRNAs). Of those, the lncRNAs are increasingly recognized for their key roles in regulation of multiple biological functions including immune response and autoimmunity (Aune et al., 2017; Zhao et al., 2018), but have yet to receive significant attention for their potential involvement in most human diseases including SLE. Recent multi-omics studies (Mo et al., 2019; Mo et al., 2017; Xia et al., 2017) also implicate alterations in complex SNP-lncRNA-mRNA interactions as important contributors to AID onset and pathogenesis, further emphasizing the importance of evaluating both mRNA and lncRNA genes as potential *cis* eGenes for SLE-associated regulatory variants.

While the aberrant expression of lncRNAs has recently been reported in multiple SLE studies (J. B. Wang et al., 2019; Y. Wang et al., 2018; Wu et al., 2019; Ye et al., 2019; Q. Zhang et al., 2019), only a few studies have implicated the lncRNAs as potential candidate genes for SLE at GWAS-identified loci (Demirci et al., 2016; Fan et al., 2020; Zhu et al., 2015). Given that most lncRNAs are relatively novel and only recently mapped to human genome, the SLE risk loci/variants warrant further exploration for their potential *cis*-regulatory effects on both mRNA and lncRNA expression. In this investigation, we performed *in silico* analyses of SLE associated loci/SNPs using the publicly available GTEx Portal (V8) tools in order to evaluate their *cis*-regulatory effects on both mRNA and lncRNA genes in in SLE-relevant immune cells/tissues (LCLs and spleen). We found that a significant number of these SNPs were found nearby (about +-250kb) to at least one *cis* lncRNA gene. Several SNPs were also found to be associated with significant expression changes of nearby lncRNA and mRNA genes. Although our analyses have revealed a large number of significant ($P$<0.05) SNP–lncRNA associations (~70), an even higher number of significant SNP–mRNA associations (>200) were detected at the same loci, and only occasionally the lncRNA(s) were the only one(s) affected by a given SNP and/or at a given locus.

The most significant ($P$<5E-03) SNP–lncRNA associations we observed in public data have included 31 SNP–lncRNA pairs (6.0E-36<$P$<4.70E-03), involving 23 lncRNAs and 20 SNPs (from 14 SLE risk loci), which represent strong candidates for our planned follow-up work on samples obtained from the patients to directly test/explore the SNP-lncRNA-mRNA interactions in SLE. Notably, for the majority of these 14 SLE loci (n=8), the *cis*-regulated lncRNA gene(s) were among the top two eGenes detected for SLE SNPs and, at nearly half of the loci, more than one lncRNA gene were among the *cis* eGenes significantly regulated by SLE SNPs, further supporting the prioritization of these highly relevant lncRNAs for future studies in order to

determine their functional relevance and precise mechanism of action in SLE. Although most of the highly significantly *cis*-regulated lncRNA genes detected for SLE risk variants in this study appeared to be novel, the top five ($P$<5E-05) have included three lncRNAs (RP11-660L16.2, AP002954.4, and RP11-563N6.6) that have already been linked to SLE and/or other AIDs in prior studies. RP11-660L16.2 was listed among the eGenes for the related SLE risk locus in the original paper (Chen et al., 2017), whereas AP002954.4 and RP11-563N6.6 were among the lncRNAs reported as the eGenes for the loci/SNPs associated with multiple other AIDs (Ricano-Ponce et al., 2016). The direction of association observed between the latter lncRNA and AID risk alleles (*cis* effect leading to up or down regulation of gene expression) was also similar across different studies/diseases, suggesting that this lncRNA would be good therapeutic target for modulation of shared pathological mechanisms across multiple AIDs. Furthermore, our analysis also similarly captured another lncRNA, NEAT1, which has already been functionally implicated in SLE (Dong et al., 2020; F. Zhang et al., 2016; Zhao et al., 2018) (see **Introduction**).

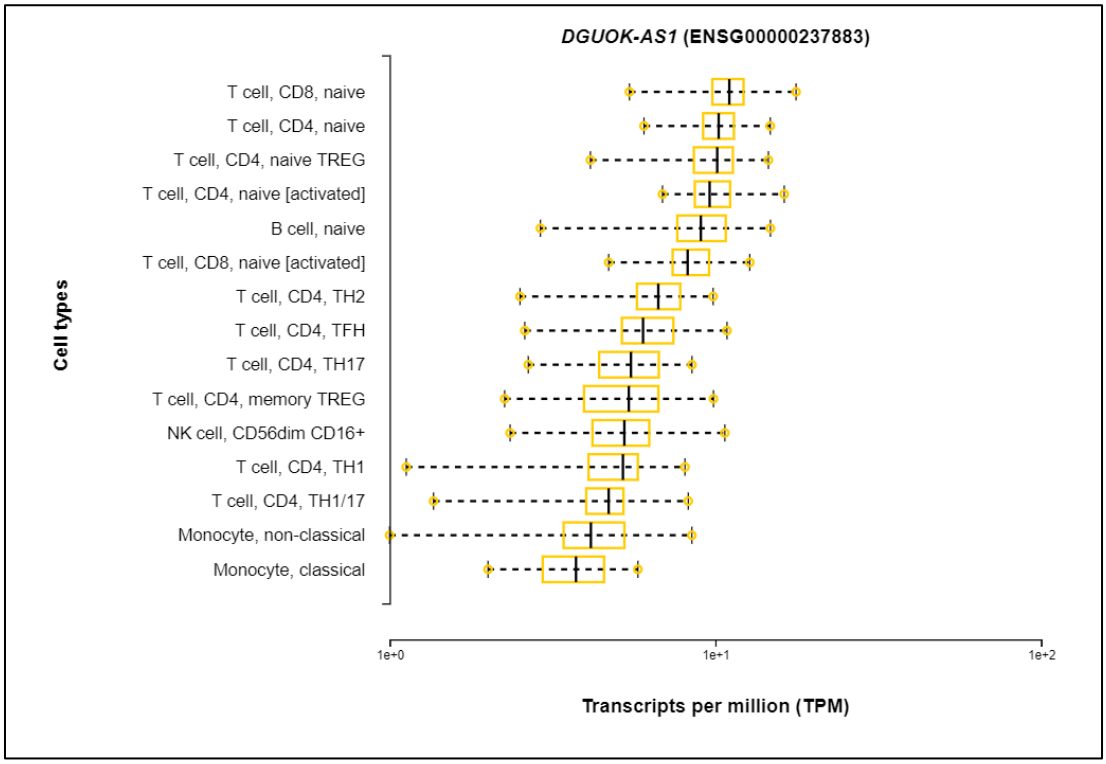
Interestingly, the majority of significant SNP–lncRNA associations were observed in the spleen followed by LCLs, and only a small number of lncRNA genes were found to be cis-regulated in both spleen and LCLs. This result may be attributed to the fact that the spleen is an organ rich with various different immune cell types while LCLs are a specifically derived line of B-cells. Consistently, when highly SLE-relevant *cis* lncRNAs (n=23) were further assessed using the DICE database (Schmiedel et al., 2018) to explore their expression patterns in 13 immune cell types & 2 activated cell types, of 18 lncRNAs detected in that data set, 5 were reported as with "low expression" but the remaining 13 showed cell type-specific expression patterns involving various immune cells (See **Appendix A** for the related figures). As expected, the expression results mostly correlated well between the GTEx and DICE data sets, such that those detected in only

spleen but not LCLs were ‘most abundantly’ expressed in immune cells other than B cells. The spectrum of different immune cell types (T cells, B cells, NK cells, monocytes) where these highly SLE-relevant lncRNAs are expressed is also in line with multiple adaptive and innate immune system abnormalities observed in SLE-related immunopathology.

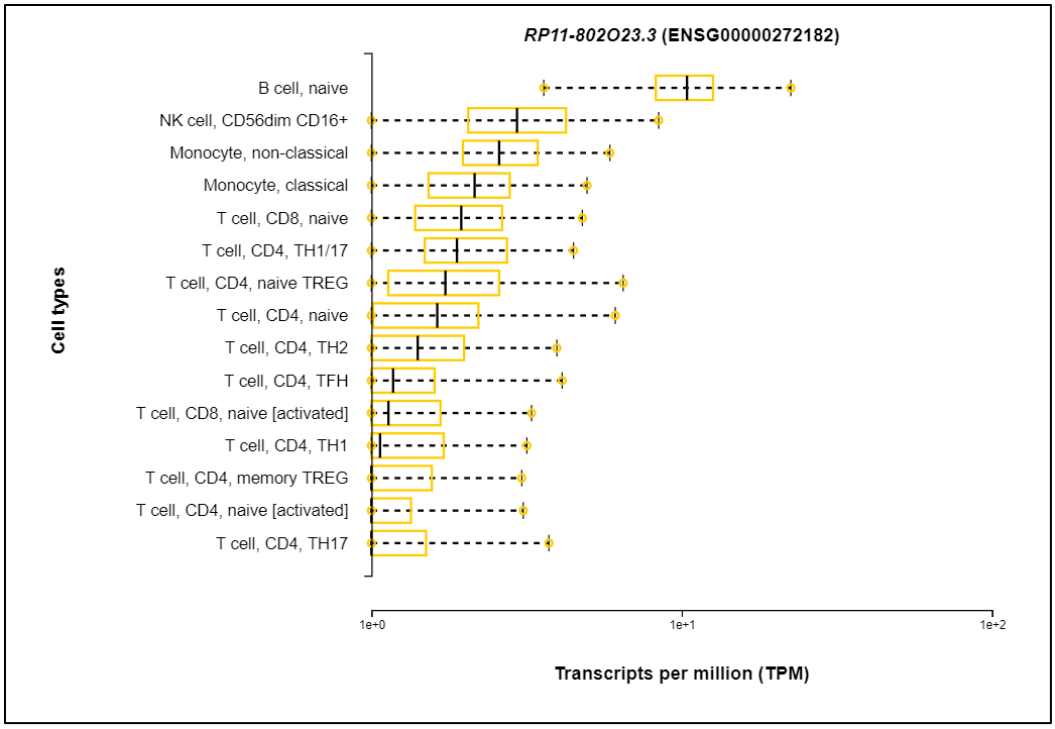
Due to the nature of this study, several notable limitations must be mentioned. Firstly, because our *in silico* study utilizes several databases and digital resources, the inconsistencies in notations between resources and evolution of data over time are major challenges to overcome. This is especially true for newly identified lncRNAs that are often subjected to name/symbol changes across different versions of reference databases. Secondly, while public tools/databases are very useful for cost-effective preliminary functional analyses, they also exhibit various limitations depending on the degree of coverage for SNPs and/or transcripts analyzed and, due to the absence of data on all healthy or diseased tissue/cell types, for instance the lack of coverage of SLE affected individuals/tissues/cells. Hence, the top SLE-relevant lncRNAs identified in this study will be further tested for functional relevance in samples obtained from SLE patients.

In summary, the results of our study provide further support for the recently proposed role of SNP-lncRNA-mRNA regulation networks in immune regulation and autoimmunity as suggested by the identification of several lncRNA genes *cis*-regulated by SLE-associated SNPs in addition to mRNA genes. LncRNAs represent exciting pharmaceutical targets due to their ability to interact with a variety of molecules to regulate gene expression hence an improved understanding of their role in SLE may guide future preventive or therapeutic interventions (Khorkova, Hsiao, & Wahlestedt, 2015).

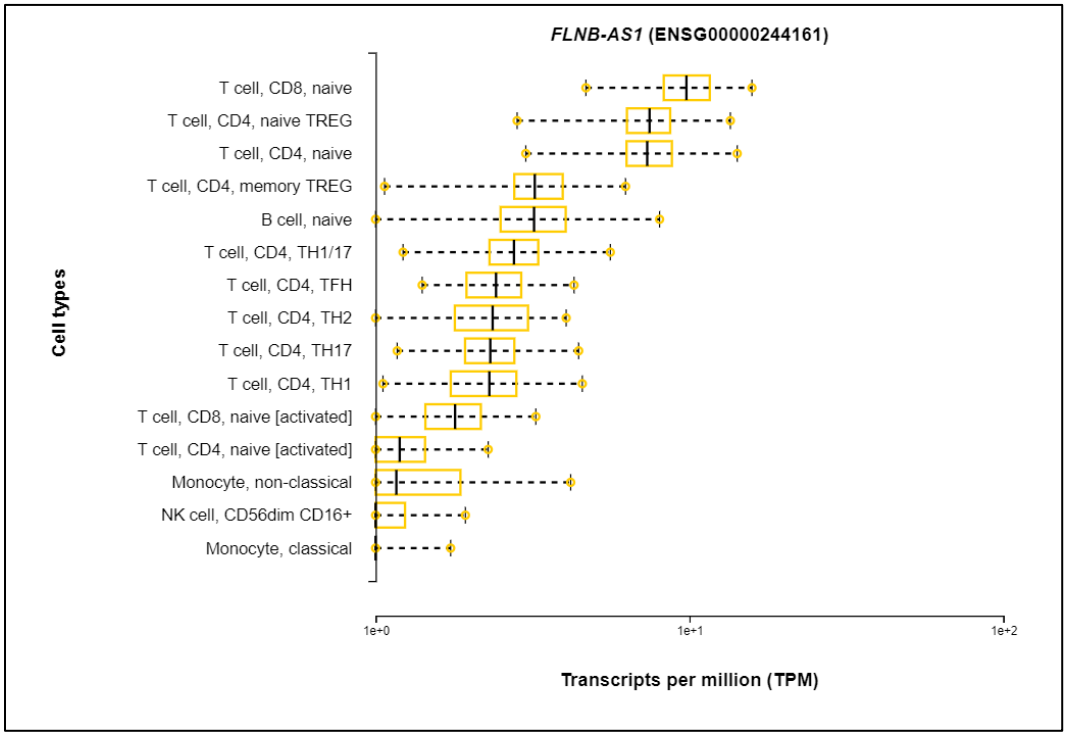
# Appendix A: DICE db Figures



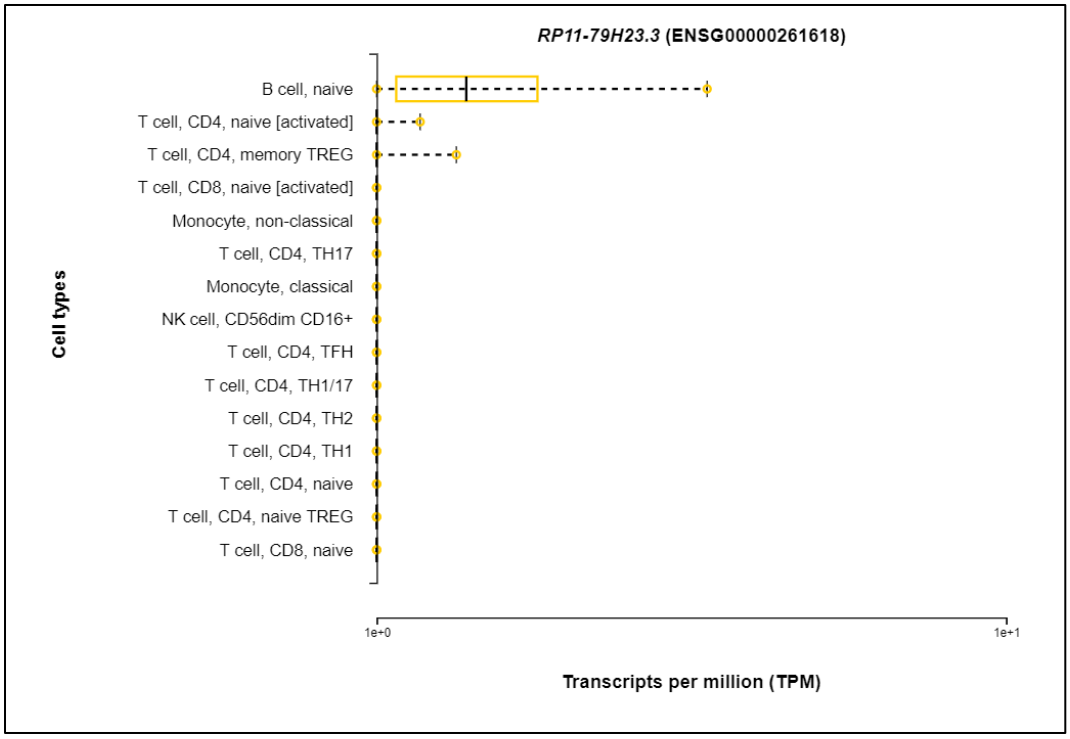

**Appendix Figure 1 DICE expression results for lncRNA DGUOK-AS1**
Graph was extracted from the DICE database using the Explore gene feature **(https://dice-database.org/landing).**



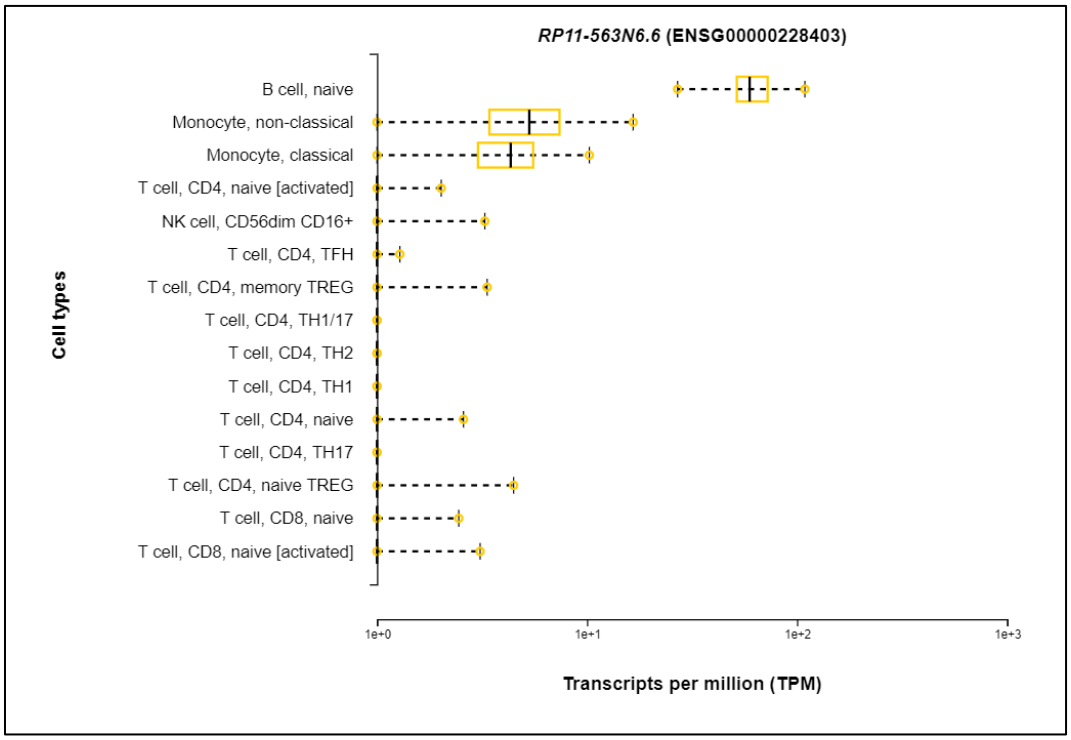

**Appendix Figure 2 DICE expression results for lncRNA RP11-802O23.3**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing**).



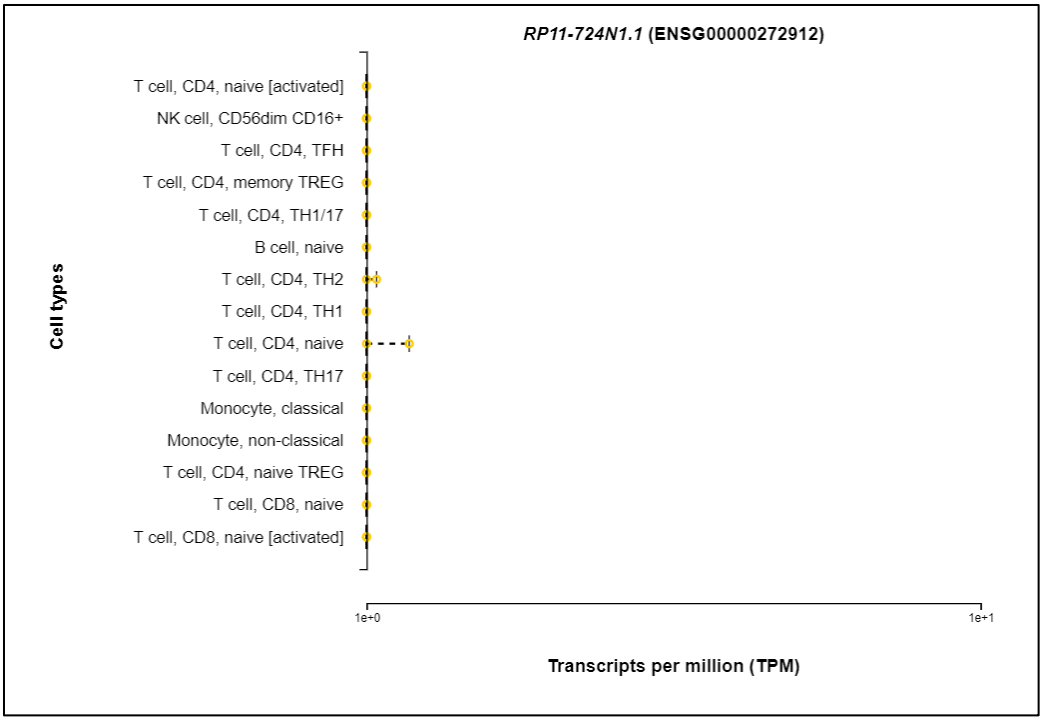

**Appendix Figure 3 DICE expression results for lncRNA FLNB-AS1**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing**).



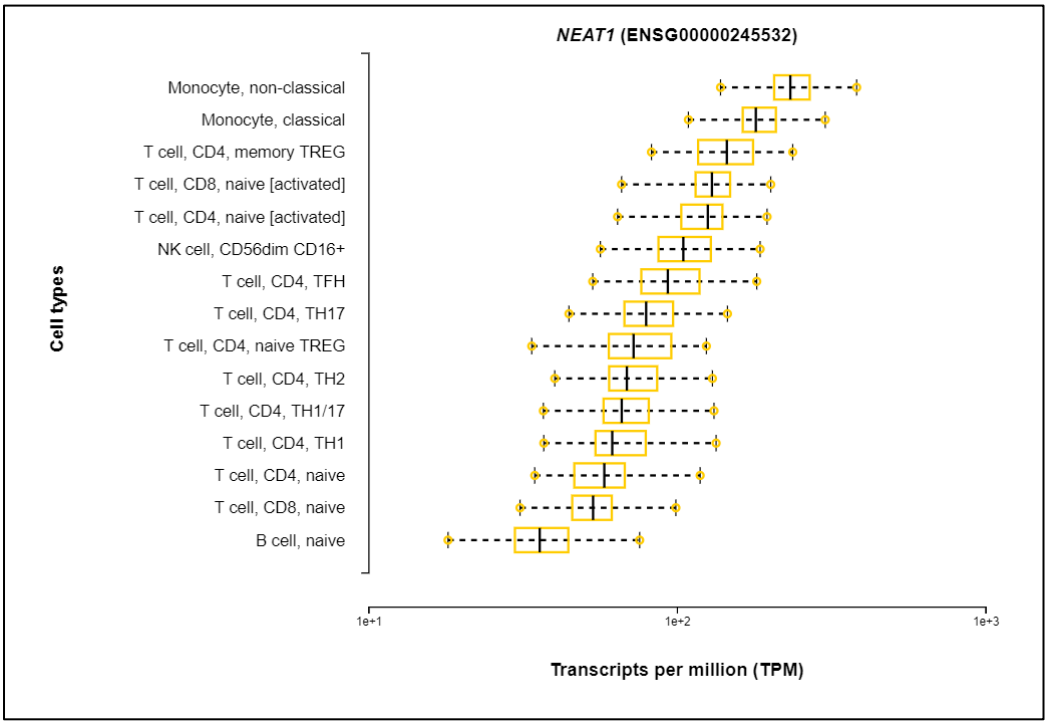

**Appendix Figure 4 DICE expression results for lncRNA RP11-79H23.3**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing).**



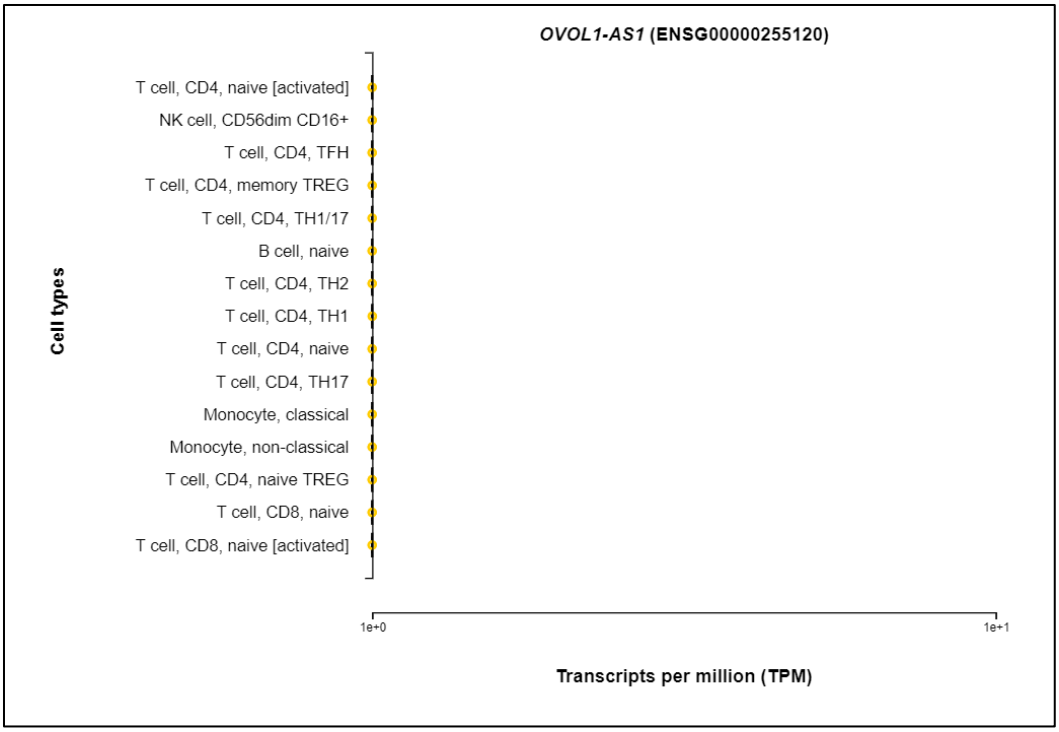

**Appendix Figure 5 DICE expression results for lncRNA RP11-563N6.6**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing).**



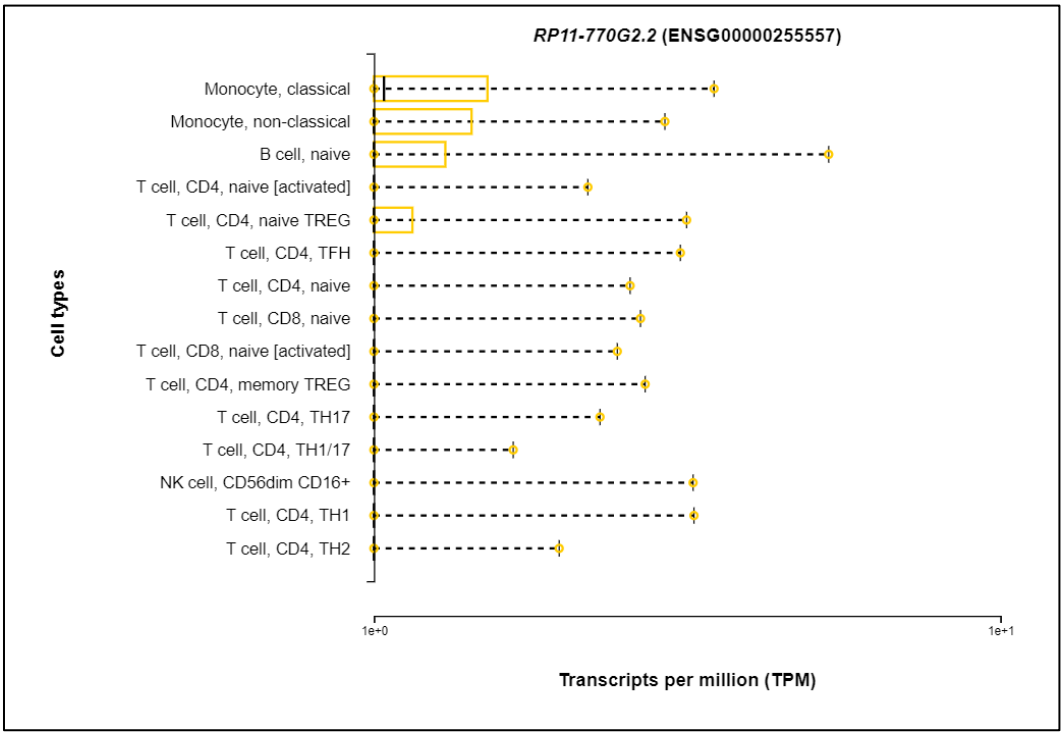

**Appendix Figure 6 DICE expression results for lncRNA RP11-724N1.1**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing**).
**This gene was maked as having low expression.**



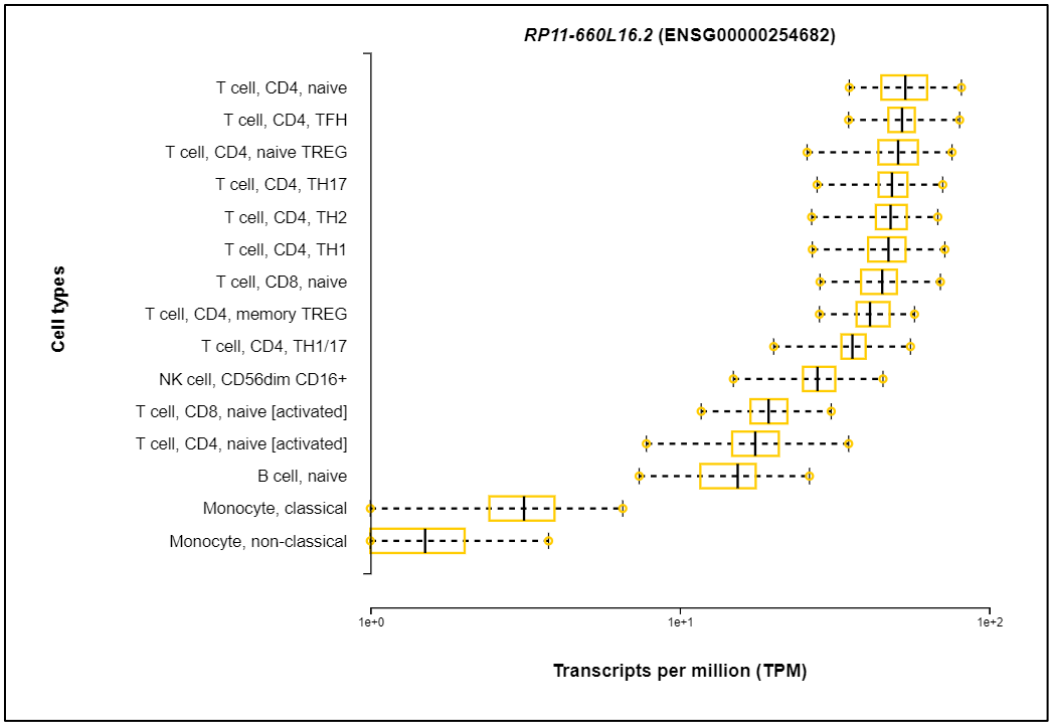

**Appendix Figure 7 DICE expression results for lncRNA NEAT1**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing**).



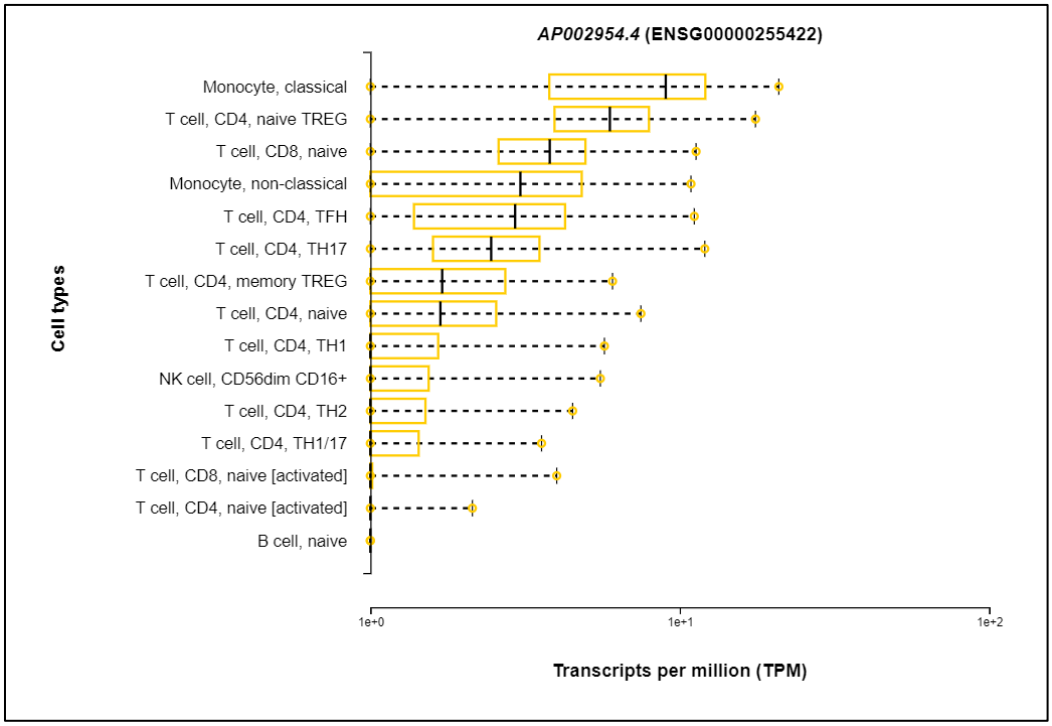

**Appendix Figure 8 DICE expression results for lncRNA OVOL1-AS1**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing**). **This gene was marked as having low expression.**



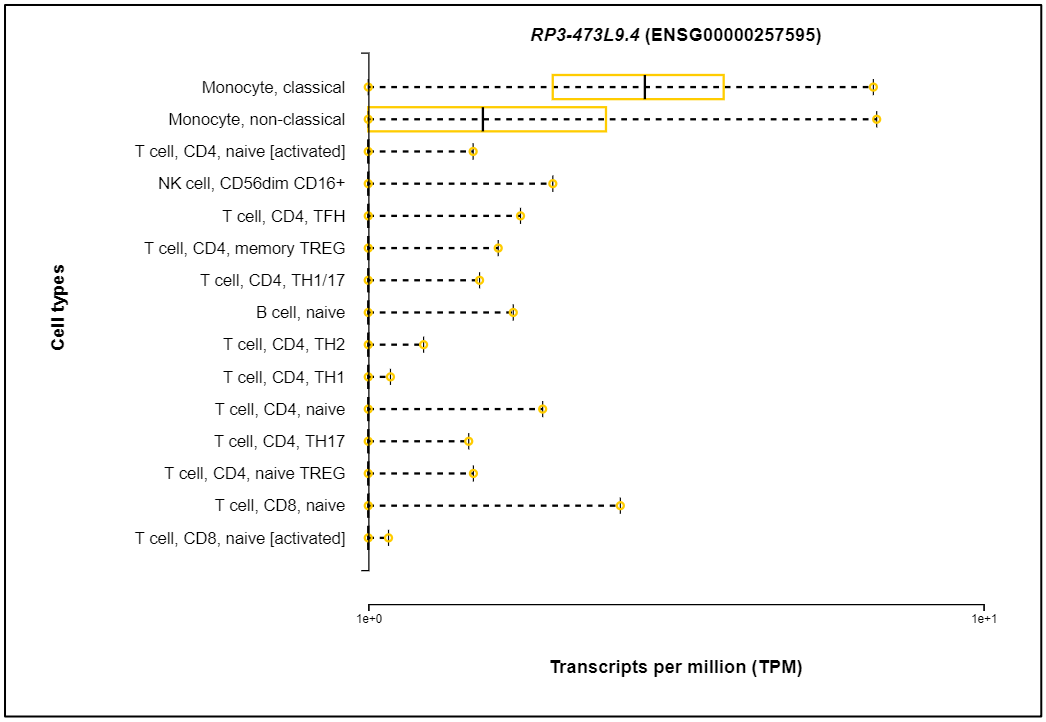

**Appendix Figure 9 DICE expression results for lncRNA RP11-700G2.2**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing**).



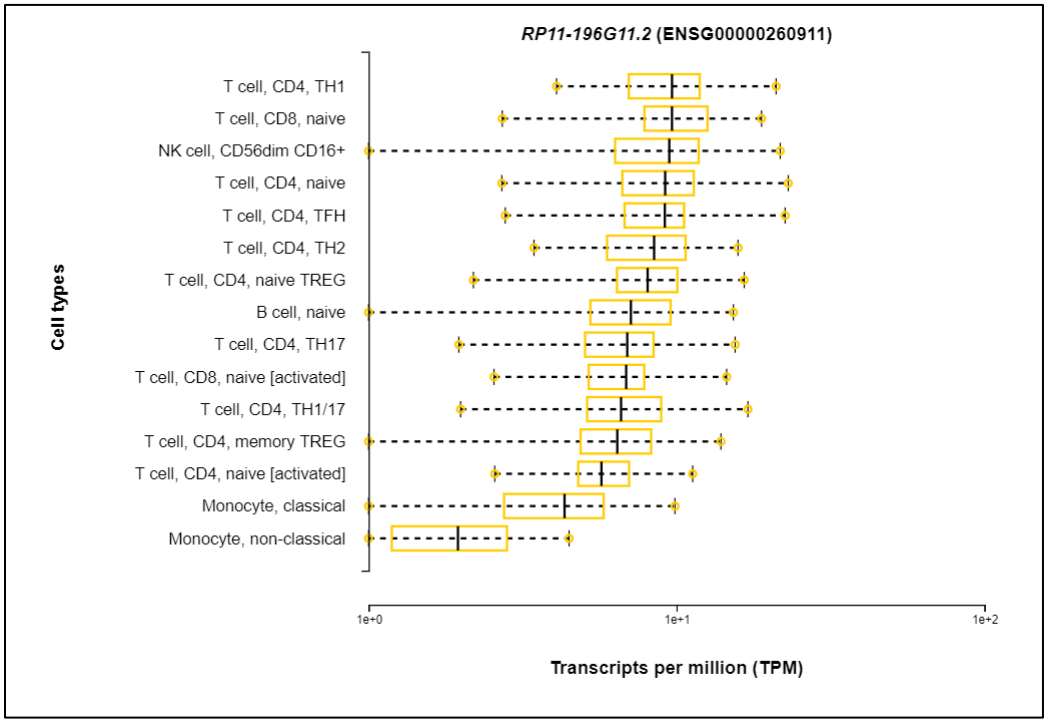

**Appendix Figure 10 DICE expression results for lncRNA RP11-660L16.2**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing).**



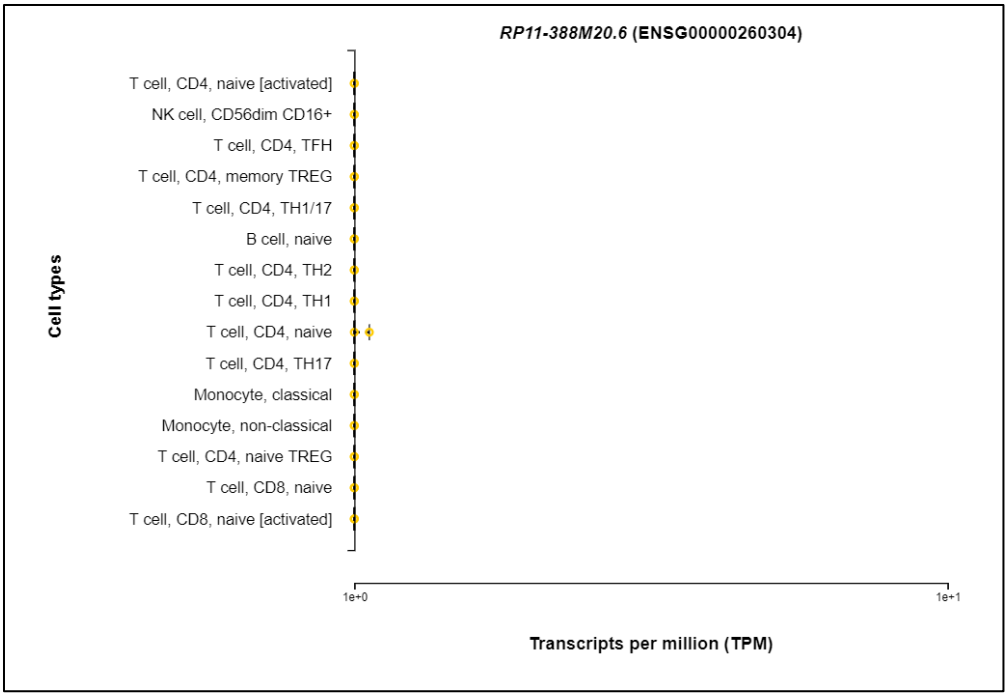

**Appendix Figure 11 DICE expression results for lncRNA AP002954.4**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing).**



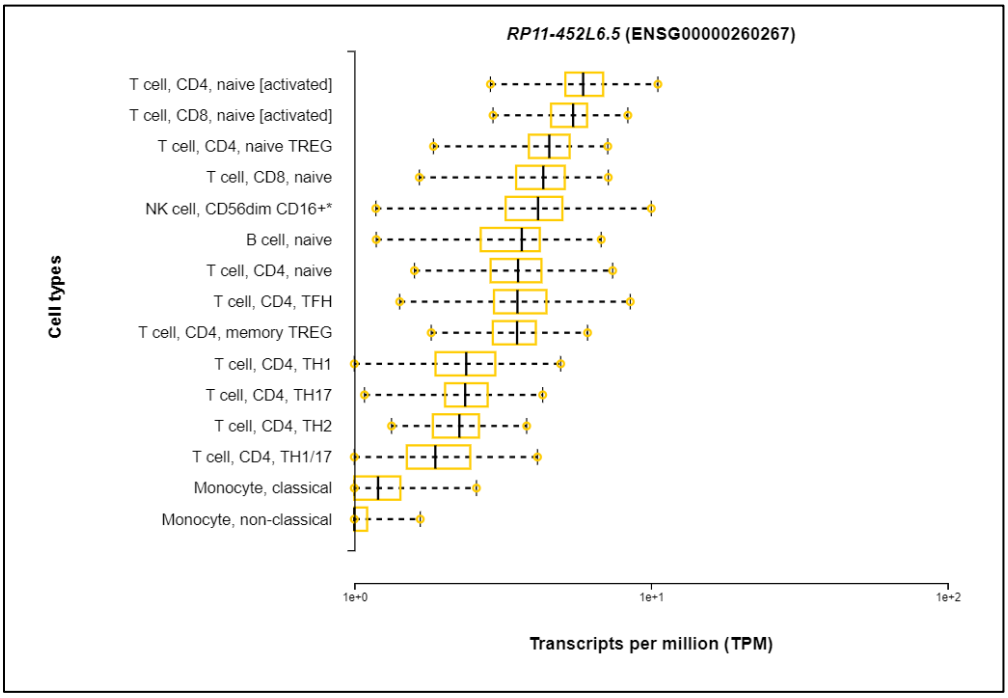

**Appendix Figure 12 DICE expression results for lncRNA RP3-473L9.4**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing).**



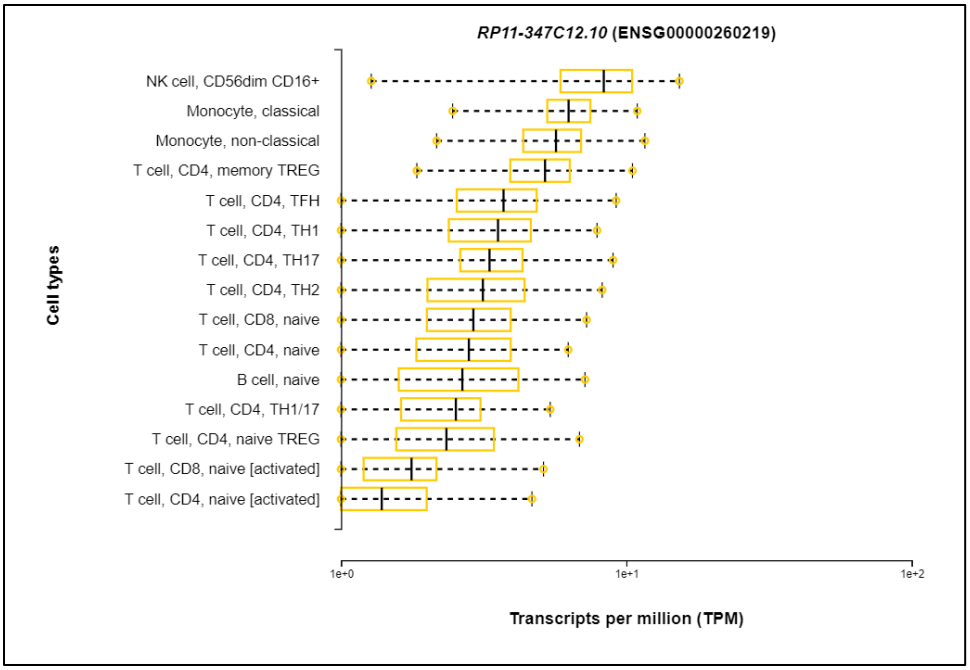

**Appendix Figure 13 DICE expression results for lncRNA RP11-196G11.2**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing).**



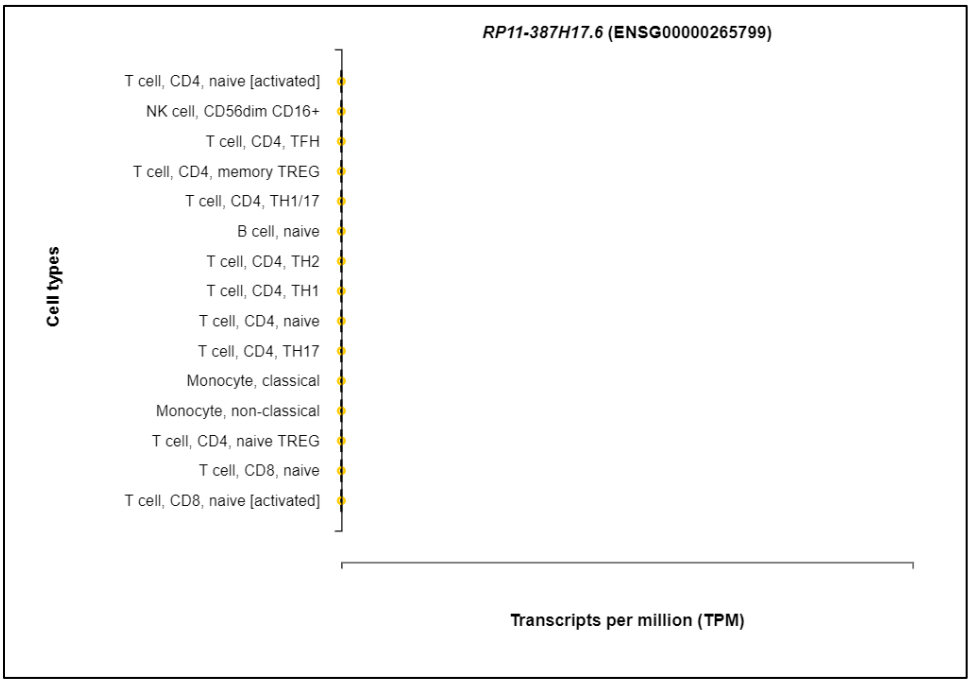

**Appendix Figure 14 DICE expression results for lncRNA RP11-388M20.6**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing**). **This gene was marked as having low expression.**



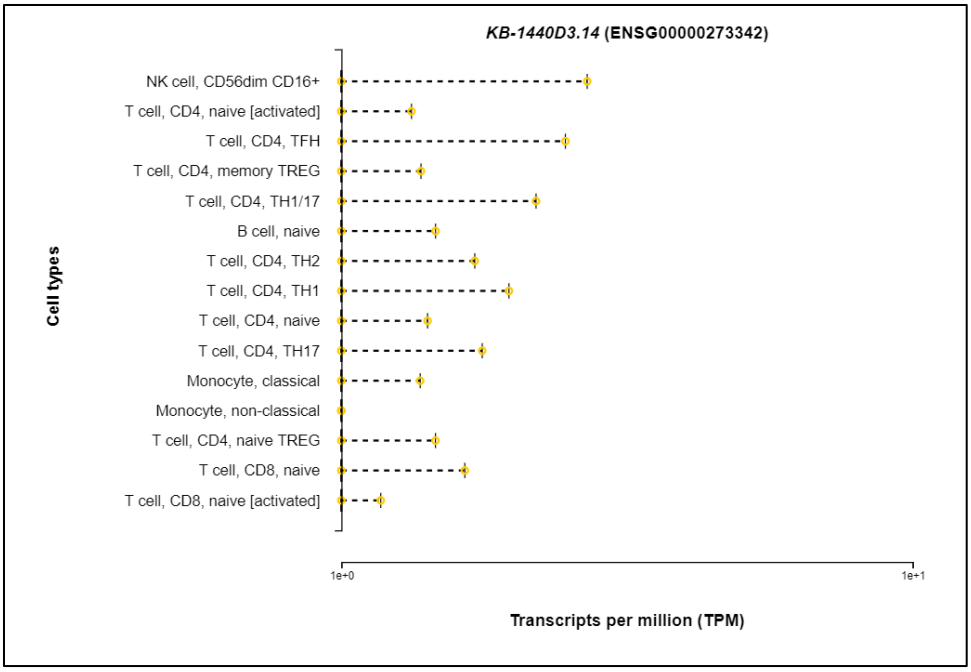

**Appendix Figure 15 DICE expression results for lncRNA RP11-452L6.5**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing**).




**Appendix Figure 16 DICE expression results for lncRNA RP11-347C12.10**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing).**




**Appendix Figure 17 DICE expression results for lncRNA RP11-387H17.6**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing).**
**This gene was marked as having low expression.**




**Appendix Figure 18 DICE expression results for lncRNA KB-1440D3.14**
Graph was extracted from the DICE database using the Explore gene feature (**https://dice-database.org/landing**). **This gene was marked as having low expression.**

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