Systemic lupus erythematosus (SLE) is a serious prototype autoimmune disease characterized by chronic inflammation, auto-antibody production and multi-organ damage. Recent association studies have identified a long list of loci that were associated with SLE with relatively high statistical power. However, most of them only established the statistical associations of genetic markers and SLE at the DNA level without supporting evidence of functional relevance. Here, using publically available datasets, we performed integrative analyses (gene relationship across implicated loci analysis, differential gene expression analysis and functional annotation clustering analysis) and combined with expression quantitative trait loci (eQTLs) results to dissect functional mechanisms underlying the associations for SLE. We found that 14 SNPs, which were significantly associated with SLE in previous studies, have cis-regulation effects on four eQTL genes (HLA-DQA1, HLA-DQB1, HLA-DQB2, and IRF5) that were also differentially expressed in SLE-related cell groups. The functional evidence, taken together, suggested the functional mechanisms underlying the associations of 14 SNPs and SLE. The study may serve as an example of mining publically available datasets and results in validation of significant disease-association results. Utilization of public data resources for integrative analyses may provide novel insights into the molecular genetic mechanisms underlying human diseases.
Gene Relationship across Implicated Loci (GRAIL)

In most situations, confidently identified loci (GRAIL) are likely to be located within the nearby region of the SNP, which often contains multiple genes. A commonly used approach for identification of candidate gene is to select nearby genes that were chosen for the analysis using the Database for Annotation, Visualization and Integrated Discovery (DAVID) integrated database query tools (http://david.abcc.ncifcrf.gov/) [25,26]. A P-value was calculated to determine whether GO term or pathway annotates a specified list of genes at a frequency greater than that would be expected by chance. Bonferroni correction was adopted for multiple testing.

Results

By searching the GWAS Integrator [15] and PheGenI [www.ncbi.nlm.nih.gov/gap/PheGenI/], we selected 135 robust genetic associations (P < 10^-7) between SLE and 128 unique SNPs (Table S1). These association results come from 8 published SLE association studies [6–13]. Some of these studies have relatively large sample sizes, e.g., the study performed by Han et al. [6] has 1,047 Chinese Han cases and 1,205 Chinese Han controls plus 3,152 Chinese Han cases and 7,030 Chinese Han controls in initial and replication analyses, respectively. As shown in Table S1, the majority of these associations (>100 associations) were mapped to the HLA region. These SLE-associated genetic variants in HLA region span ~6.4 Mbp length according to the physical location at chromosome 6p21.3.

As shown in Table S1, 7 SNPs have replication associations in multiple independent studies, e.g., rs7574865 in the intron region of STAT4 gene was significantly associated with SLE (P = 5.0E-42, and P = 2.0E-20) in two independent studies. The columns “Gene 1” and “Gene 2” listed the genes physically located at two sides of the SNP, respectively. About 30 “susceptible” genes detected by GRAIL analysis, as listed in the column “implicated genes” of Table S1, are overlapped with the genes identified according to the physical positions (Columns “Gene 1” and “Gene 2”). The above two methods identified a total of 108 unique candidate genes, which were subject to further analyses.

EQTQL analysis is an important approach in detection of functional mechanism underlying association by testing whether identified variants at the DNA level may lead to variations in mRNA expression of nearby genes. Among the 128 unique SNPs, we found that about 61 SNPs have potential eQTL effects either on the “identified” genes or on other genes (Table 1 and Table S2). Fifty-five associations between 23 unique SNPs and expression of 11 “identified” genes from the list of Table S1 [108 genes in total] were detected (Table 1) in monocytes and LCLs, which are two types of cells closely correlated with immune response. Among the 23 unique SNPs, only three were located at non-HLA regions. The entire 23 unique SNPs act as cis-effect regulators of the 11 “identified” genes. Especially, nine SNPs around HLA-DQB1 gene showed strong associations with expression level of HLA-DQB1 gene in two cell groups (LCLs and monocytes). Six SNPs (rs7192, rs9268832, rs9275224, rs2647012, rs9275572, and rs9275596), which extend more than 240 kb, were associated with the expression of HLA-DRA gene.

Furthermore, we performed differential expression analyses for the 11 identified eQTL genes in multiple SLE related cells: macrophages, mononuclear cells, and peripheral blood cells (Table 2). T-tests showed that four genes (HLA-DQA1, HLA-DQB1, HLA-DQB2, and IRF5) were differentially expressed in samples S1 or S3 (Table 2).

The above functional evidence, taken together, highlighted the significance of 14 SLE-associated SNPs, i.e., the first 14 SNPs listed in Table 1, as these SNPs serve as cis-effect regulators of four SLE-associated genes (HLA-DQA1, HLA-DQB1, HLA-DQB2, and IRF5), which also were differentially expressed in SLE-related cell groups. Functional analysis using FASTSNP program [24] found that the rs2187669 in the intron of HLA-DQA1 was possible transcriptional binding sites for intronic enhancers. Therefore, the SNP may regulate transcription by altering binding
Table 1. Expression quantitative trait locus (eQTL) analysis results between SNPs and the expressions of 11 genes from the 108 “identified” genes.

| SNP ID   | Chr. Location | Allele | Role      | Association P-value | Gene 1   | Gene 2   | Implicated Gene | eQTL gene | Effect | Score | Target | Ref.  |
|----------|---------------|--------|-----------|---------------------|----------|----------|-----------------|-----------|--------|-------|--------|-------|
| rs4728142 | chr7          | 128573967 | A/G       | unknown             | 8.00E-19 | KCP      | IRF5           | IRF5      | eqtl   | 130.5 | Monocytes | [18] |
| rs1573649 | chr6          | 32731258 | C/T       | 5'utr               | 2.00E-10 | HLA-DQB2  | HLA-DQB2       | HLA-DQB2  | PP-eqtl | 0.1   | LCLs   | [19]  |
| rs603130  | chr6          | 32732210 | A/G       | upstream            | 4.43E-10 | HLA-DQB2  | HLA-DQB2       | HLA-DQB2  | PP-eqtl | 0     | LCLs   | [19]  |
| rs16898264| chr6          | 32677152 | A/G       | unknown             | 3.85E-09 | HLA-DQA2  | HLA-DRA        | HLA-DQB1  | exonQTL | 4.4   | LCLs   | [22]  |
| rs2647012 | chr6          | 32664458 | A/G       | unknown             | 1.27E-13 | HLA-DQB1  | HLA-DQA2       | HLA-DRA   | exonQTL | 6.9   | LCLs   | [22]  |
| rs2647050 | chr6          | 32669767 | C/T       | unknown             | 5.38E-09 | HLA-DQB1  | HLA-DQA2       | HLA-DRA   | exonQTL | 4.4   | LCLs   | [22]  |
| rs2856717 | chr6          | 32670308 | C/T       | unknown             | 1.03E-13 | HLA-DQB1  | HLA-DQA2       | N/A       | eqtl    | 33.9  | Monocytes | [18] |
| rs2856718 | chr6          | 32670255 | A/G       | unknown             | 5.33E-09 | HLA-DQB1  | HLA-DQA2       | HLA-DRA   | exonQTL | 4.4   | LCLs   | [22]  |
| rs2856725 | chr6          | 32666738 | A/G       | unknown             | 1.11E-13 | HLA-DQB1  | HLA-DQA2       | N/A       | exonQTL | 6.4   | LCLs   | [22]  |
| rs2858305 | chr6          | 32670464 | A/C       | unknown             | 7.88E-14 | HLA-DQB1  | HLA-DQA2       | N/A       | exonQTL | 6.8   | LCLs   | [22]  |
| rs9275572 | chr6          | 32678999 | A/G       | unknown             | 6.41E-14 | HLA-DQB1  | HLA-DQA2       | HLA-DQB1  | eqtl    | 24.3  | Monocytes | [18] |
| rs9275596 | chr6          | 32681631 | C/T       | unknown             | 3.33E-16 | HLA-DQB1  | HLA-DQA2       | HLA-DRA   | exonQTL | 5.3   | LCLs   | [22]  |
| rs2187668 | chr6          | 32605884 | A/G       | intron              | 6.00E-28 | HLA-DQA1  | HLA-DQA1       | HLA-DQB2  | eqtl    | 34.6  | Monocytes | [18] |
| rs9271100 | chr6          | 32576478 | C/T       | unknown             | 1.00E-12 | HLA-DRB1  | HLA-DQA1       | N/A       | eqtl    | 4.3   | LCLs   | [22]  |
| rs394061  | chr6          | 30321189 | G/T       | unknown             | 1.24E-09 | HLA-N     | UBQLN1P1       | IER3      | eqtl    | 33.6  | Monocytes | [18] |
| rs9271100 | chr6          | 32576478 | C/T       | unknown             | 1.00E-12 | HLA-DRB1  | HLA-DQA1       | N/A       | eqtl    | 15.2  | LCLs   | [22]  |
| rs2647012 | chr6          | 32664458 | A/G       | unknown             | 1.27E-13 | HLA-DQB1  | HLA-DQA2       | HLA-DRA   | transcriptQTL | 4.5 | LCLs   | [22]  |
| rs7192    | chr6          | 32411646 | G/T       | missense            | 2.02E-10 | HLA-DRA   | HLA-DRA        | HLA-DRA   | transcriptQTL | 9  | LCLs   | [22]  |
| rs9268832 | chr6          | 32427789 | C/T       | unknown             | 1.53E-10 | HLA-DRB9  | HLA-DRB9       | HLA-DRA   | transcriptQTL | 9.5 | LCLs   | [22]  |
| SNP ID  | Chr  | Location    | Allele | Role   | Association | Score  | Target | Ref.     |
|---------|------|-------------|--------|--------|-------------|--------|--------|----------|
| rs9275224 | chr6 | 32659878    | A/G    | unknown| 4.45E-12    | HLA-DQB1 | HLA-DQA2 | HLA-DRA  | transcriptQTL | 4 | LCLs | [22] |
| rs9275572 | chr6 | 32678999    | A/G    | unknown| 6.41E-14    | HLA-DQB1 | HLA-DQA2 | HLA-DRA  | eqtl     | 40.1 | Monocytes | [18] |
| rs9275596 | chr6 | 32681631    | C/T    | unknown| 3.33E-16    | HLA-DQB1 | HLA-DQA2 | HLA-DRA  | transcriptQTL | 5.1 | LCLs | [22] |
| rs2647012 | chr6 | 32664458    | A/G    | unknown| 1.27E-13    | HLA-DQB1 | HLA-DQA2 | HLA-DRA  | transcriptQTL | 4.2 | LCLs | [22] |
| rs2856725 | chr6 | 3266738     | A/G    | unknown| 1.11E-13    | HLA-DQB1 | HLA-DQA2 | N/A      | transcriptQTL | 4.2 | LCLs | [22] |
| rs2858305 | chr6 | 3270464     | A/C    | unknown| 7.88E-14    | HLA-DQB1 | HLA-DQA2 | N/A      | transcriptQTL | 4.1 | LCLs | [22] |
| rs9271100 | chr6 | 32576478    | C/T    | unknown| 1.00E-12    | HLA-DRB1 | HLA-DQA1 | N/A      | eqtl     | 93   | LCLs | Database    |
| rs1327713 | chr8 | 11349186    | A/G    | unknown| 1.00E-10    | FAM167A  | BLK     | BLK      | exonQTL  | 6.4   | LCLs | [22] |
| rs1127317 | chr6 | 26372786    | A/G    | intron  | 6.83E-10    | BTN3A2   | BTN3A2  | BTN3A2  | eqtl     | 21.4  | LCLs | [19] |
| rs9379858 | chr6 | 26367689    | C/T    | intron  | 6.21E-10    | BTN3A2   | BTN3A2  | BTN3A2  | eqtl     | 21.4  | LCLs | [20] |
| rs9379859 | chr6 | 2636949     | C/T    | intron  | 3.79E-10    | BTN3A2   | BTN3A2  | BTN3A2  | eqtl     | 21.4  | LCLs | [20] |

Note: N/A:not available; “Score”: –log10 (P); LCLs: lymphoblastoid cell lines; transcript-QTL: transcript expression levels against SNPs; exon-QTL: quantified reads for known exons by RNA sequencing against SNPs; sQTL: splicing QTL; PP-eqtl: posterior probability-eqtl.
All the eqtls have cis-effects.
Database #: http://eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl.
*Gene 1* and *Gene 2* are the nearby genes physically located at two sides of SNP.
*GRAIL P-value* and *Implicated gene* are the results from Gene Relationships Across Implicated Loci (GRAIL) analyses.
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Table 2. Differential expression analyses for the detected eQTL genes in multiple SLE related cells.

| Sample | S1   | S2   | S3   |
|--------|------|------|------|
| Disease| SLE  | SLE  | SLE  |
| Target cells | Macrophages | Mononuclear cells | Peripheral blood cells |
| Sample size | 20:16 | 20:16 | 21:45 |
| Platform | Illumina HumanHT-12 V4.0 expression beadchip | Illumina HumanHT-12 V4.0 expression beadchip | Hitachisof AceGene Human Oligo Chip 30K 1 Chip |
| Ref. | Database# | Database# | [14] |
| GSE NO. | GSE37356 | GSE37356 | GSE20864 |

| Gene symbol | Probe ID | T-test P-value | SLE/control | Probe ID | T-test | SLE/control | Probe ID | T-test P-value | SLE/Control* |
|-------------|----------|----------------|-------------|----------|--------|-------------|----------|----------------|--------------|
| HLA-DQA1    | ILMN_1808405 | 3.10E-01 | 1.04 | ILMN_1808405 | 6.86E-01 | 1.01 | AGhsA101413 | 4.88E-02 | 16.19048 |
| HLA-DQB1    | ILMN_1661266 | 6.99E-01 | 1.02 | ILMN_1661266 | 9.83E-01 | 1 | AGhsA030823 | 4.77E-02 | 6.2/5.08 |
| HLA-DQB2    | ILMN_1741648 | 2.49E-02 | 1.01 | ILMN_1741648 | 6.25E-02 | 0.99 | N/A | N/A | N/A |
| IRF5        | ILMN_1670576 | 5.67E-01 | 0.98 | ILMN_1670576 | 5.68E-01 | 0.98 | AGhsB110506 | 1.62E-02 | 8.89/5.95 |

Note: Sample size: SLE cases: controls; N/A: Not available; *ratio of mean expression values of log2(sample/reference).

GSE NO: Gene Expression Omnibus Number, www.ncbi.nlm.nih.gov/geo/.
Database#: The data downloaded from the database (www.ncbi.nlm.nih.gov/geo/) according to GSE number.
We only listed the most significant expression results of probes if one gene has multiple detected probes.
doi:10.1371/journal.pone.0053037.t002
sites for transcription factors or by increasing or decreasing the affinity of binding for transcription factors. Functions for the other 15 SNPs are unknown yet.

To test the probability of our “identified” genes clustering into a particular biological pathway and GO term, we performed a functional annotation clustering analysis using functional annotation tool of DAVID database. We found significant GO terms and KEGG pathways even after Bonferroni correction. The “identified” genes tend to enrich in immune-related pathways (such as “autoimmune thyroid disease”, “Intestinal immune network for IgA production”, and “immune response”) [data not shown]. Especially, we found a significant clustering (Bonferroni correction P = 8.00E-06) of 9 genes (HLA-DQB1, TNF, HLA-DRB1, HIST1H2AH, HLA-DOB, HLA-DQA2, HLA-DQA1, HLA-DRA) directly involved in SLE. Among the 11 identified eQTL genes, five genes (HLA-DQB1, HLA-DRB1, HLA-DQA2, HLA-DQA1, HLA-DRA) were significantly clustered in multiple immune related KEGG pathways or GO terms (Table S3).

**Discussion**

By using publicly available datasets, this study performed integrative analyses and combined with eQTL results to detect functional mechanisms underlying the associations for SLE. We discovered 23 SNPs acting as cis-effect regulators on 11 “identified” genes. Four eQTL genes have differential expression signals in the SLE-associated cells or tissues. The “identified” genes tend to enrich in KEGG Pathways (autoimmune thyroid disease, intestinal immune network for IgA production, and immune response), which are very closely relevant to SLE.

In biologic systems, genetic information carried by DNA is passed on to RNA molecules via transcription and then to protein molecules through translation. Sequence variants at the DNA level represent a class of heritable molecules and contribute to variability of complex traits in the population. The functional mechanisms underlying associations between variants at the DNA level and SLE may be that DNA sequence variants lead to variation in quantifiable intermediate phenotypes (such as RNA level), which subsequently lead to variation of susceptibility to SLE. Therefore, integrating substantial evidences from multiple levels (i.e., DNA, RNA) could ascertain potential functioning mechanism of genes and their contribution to variation in susceptibility to SLE.

Recent association studies have identified a long list of loci that were associated with SLE with relatively high statistical power. A majority of these associations (>100 associations) were mapped to the HLA region. It is well-known that there is strong linkage disequilibrium (LD) at HLA region. It is reasonable to infer that the significant signals for some of the genetic markers may be due to their strong LD with true functional variants within the HLA region. As shown in Results section, multiple SNPs, extending a relatively long distance (240 kb), were consistently associated with the expression of HLA-DRA. Strong LD at HLA region may partially contribute to this observation.

HLA-DQA1, HLA-DQB1, and HLA-DQB2 are HLA class II genes involved in immune response. Class II molecules are heterodimers consisting of an alpha (DQA) and a beta chain (DQB), both anchored to the membrane, which play a central role in the immune system by presenting peptides derived from extracellular proteins. These genes have been found to consistently associate with SLE in several populations [7,8] at DNA level, though functions for these genes and mechanism for the observed associations were not studied. The functional evidence from this study, taken together, suggested potential regulatory mechanisms underlying the associations between SLE and the associated SNPs.

Briefly, different genotypes of the SNPs, by regulating differential mRNA transcriptions of functional genes (HLA-DQA1, HLA-DQB1, and HLA-DQB2) and thus differential protein expression and enzyme activity, consequently effect on variation of susceptibility to SLE in the population.

Interferon (IFN) regulatory factor 5 (IRF5) is a pivotal transcription factor in the type I IFN pathway, which regulates inflammatory cytokines, expression of IFN-dependent genes, and genes involved in apoptosis. Previous studies identified IRF5 as one of the most strongly and consistently SLE-associated loci outside the HLA region. Four functional variants in IRF5 were identified in multiple ethnic groups: a 5 bp indel (insertion–deletion) near the 3′ untranslated region (UTR), rs2004640 in the first intron, a 30 bp indel in the sixth exon, and rs10954213 in the 3′ UTR [27–35]. In addition, a SNP, rs4720142, located 10 kb downstream of IRF5 gene, was highly strongly associated with SLE (P = 8.00E-19) [6]. In the eQTL analysis, this SNP was consistently and highly associated with expression of IRF5 gene in both monocytes (P<1E-120) [10] and lymphoblastoid cell lines (P<1E-06) [90]. Compared with GG genotype at rs4720142, AA genotype individuals tend to have higher IRF5 expression levels.

The combined evidence from association analyses, eQTL analyses, and differential expression analyses suggested that the rs4720142 or other nearby genetic variant contribute significant to variation of susceptibility to SLE in the population.

To be noted, failure to find functional evidence underlying the selected associations through mining publicly available data and results does not necessarily exclude the importance of the associations with SLE, given that (1) absence of association between SLE-associated SNP and mRNA expression may result from limited statistical power due to small sample size or small effect of the SNP; (2) the associated genes may exert effects on SLE through other tissues or cells not studied herein; (3) sequence variant in a gene may lead to SLE by other mechanisms (e.g., epigenetic regulation) instead of regulating gene expression. In-depth functional studies are required, which may provide novel insights into mechanisms underlying the associations detected at DNA level.

In addition, this exploratory pilot study has two potential limitations. First, although we gained some functional evidence for the associations between SLE and 14 SNPs, based on the current available evidence, it is very challenging to discriminate causal variants with nearby SNPs with potential functional effects, especially for SNPs at the HLA region where there is strong LD. Second, although we used two methods to select the potential genes involved in associations (gene selection according to the physical location and GRAIL analysis based on previous literature), this study does not exclude the possibility that other genes around the SNPs are also directly involved in the association around SNPs.

In summary, the functional evidence gained in this study, taken together, supports and highlights the significance of 14 SLE-associated SNPs. These SNPs act as cis-effect regulators to regulate expression of genes that were found differentially expressed between SLE patients and controls. The above evidence laid a supporting clue for us to pursue in-depth validation studies to dissect their involvements and molecular functional mechanisms in SLE. This study sets an example of mining publicly available datasets and results to validate significant disease-association results. Utilization of public data resources for integrative analyses may provide novel insights into the molecular genetic mechanisms underlying human diseases.
Supporting Information

**Table S1**
The selected association results (p<10−7) from previous 8 published studies. Note: N/A: not available; PMID: PubMed ID. “Gene 1” and “Gene 2” are the nearby genes physically located at two sides of SNP, “GRAIL p-value” and “Implicated gene” are the results from Gene Relationships Across Implicated Loci (GRAIL) analyses. * associated with anti-dsDNA negative SLE; #associated with anti-dsDNA positive SLE. (XLS)

**Table S2**
Results of eQTL analyses for the selected significant SLE-associated SNPs that have eQTL effects not on the corresponding “identified” genes but on other genes. Note; N/Anot available; “Score”: −log10 (P); LCLC: lymphoblastoid cell lines; transcript-QTL: transcript expression levels against SNPs; exon-QTL: quantified reads for known exons by RNA sequencing against SNPs; eQTL: splicing QTL; PP-eqtl: posterior probability-eqtl; Database#: http://eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl; PMID for eQTL: PubMed ID for eQTL results. “Gene 1” and “Gene 2” are the nearby genes physically located at two sides of SNP. “GRAIL p-value” and “Implicated gene” are the results from Gene Relationships Across Implicated Loci (GRAIL) analyses. (XLS)

**Table S3**
Functional annotation clustering analysis for the eQTL genes. Note: Functional annotation clustering analysis was performed using functional annotation tool of DAVID database. (DOCX)

**Author Contributions**
Conceived and designed the experiments: SFL FYD. Analyzed the data: FYD YHZ. Wrote the paper: FYD ZLZ YFG SFL.

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