Integrative analysis of mRNA and miRNA expression profiles in oral lichen planus: preliminary results

Junjun Chen, PhD,[a,b] Guanhuan Du, PhD,[a] Yufeng Wang, PhD,[a] Linjun Shi, PhD,[a] Jun Mi, PhD,[b] and Guoyao Tang, PhD[a]

Objective. Oral lichen planus (OLP), a chronic inflammatory disease of unknown etiology, is considered a potentially malignant oral disorder. The aim of the present study was to analyze candidate microRNAs (miRNAs) and genes from patients with OLP and healthy controls (HCs).

Study Design. Biopsy specimens of the oral mucosa were collected from patients with OLP (n = 9) and from HCs (n = 4). Differentially expressed miRNAs and differentially expressed genes were screened by using next-generation sequencing with DESeq and edgeR software algorithms.

Results. A total of 94 differentially expressed miRNAs and 599 differentially expressed genes were detected in OLP. Potential regulatory miRNAs and genes were obtained by analyzing miRNA–messenger RNA networks. Of these, 5 downregulated miRNAs—Hsa-miR-135 a-5 p ($P = .33$), hsa-miR-128-3 p ($P = .03$), hsa-miR-218-5 p ($P = .01$), hsa-miR-125 a-5 p ($P = .01$), and hsa-let-7 e-5 p ($P = .04$)—were the most promising biomarkers in patients with OLP compared with HCs. The identified differentially expressed genes were significantly enriched in "inflammatory" events and immune-related terms through Kyoto Encyclopedia of Genes and Genomes and Gene Ontology analysis.

Conclusions. The integrative analysis of messenger RNA and miRNA profiles provides important information to elucidate gene expression mechanisms and a comprehensive perspective to study the etiology and pathogenesis of OLP. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;124:390–402)

Oral lichen planus (OLP) is a chronic, T cell–mediated inflammatory, autoimmune mucosal disease affecting 0.1% to 4% of the general population.[1-3] The clinical presentation of OLP ranges from asymptomatic reticular white lichen to symptomatic atrophic–erosive red lichen, and reticular OLP is the most common type. Although several molecular hypotheses have been proposed with the participation of genetic, psychological, and infectious factors,[4] the pathogenesis of OLP and the factors that determine its development remain largely unknown.[5] In 2005, the World Health Organization classified OLP as a potentially malignant oral disorder[6,7] because 1.63% of lesions initially diagnosed as OLP evolve into oral squamous cell carcinomas.[8,9] Therefore, elucidating the etiopathogenic mechanisms underlying OLP and the premalignant transformation to OLP are important to facilitate accurate diagnosis and effective therapies for OLP.

MicroRNAs (miRNAs) are a class of single-stranded noncoding RNAs of approximately 21 to 25 nt in length that repress gene expression by binding to recognition sequences located in the 3′ untranslated region of target messenger RNAs (mRNAs).[10] Because of the exponential increase in the number of publications related to miRNA profiling in human tumors[11] and the pivotal role of miRNAs in the regulation of different processes (e.g., inflammation, immunity[12-14]), miRNAs rank among the top candidate biomarkers and represent a promising strategy for the early detection and accurate diagnosis of many diseases. Recently, it has become evident that miRNAs play an important role in the pathogenesis of OLP. For instance, the increased expression of miR-146a in OLP lesions may be attributed to the nuclear factor (NF)-κB–related upregulation of the

Statement of Clinical Relevance

The present study aimed to elucidate the development and progression of oral lichen planus lesions. Potential regulatory microRNAs and genes were obtained by analyzing microRNA–messenger RNA networks. The integrative analysis of messenger RNA and micro-RNA profiles provides important information to elucidate gene expression mechanisms and a comprehensive perspective to study the etiology and pathogenesis of oral lichen planus.

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[a]Department of Oral Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.
[b]Department of Biochemistry and Molecular Cell Biology, Shanghai Key Laboratory of Tumor Microenvironment and Inflammation, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

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inflammatory cytokine tumor necrosis factor α, which is involved in local immune disorders and the persistent inflammation in OLP.[15] Hu et al. showed a negative correlation between miR-125a content and the severity of OLP in different clinical forms.[16] Therefore, screening key miRNAs could be valuable for understanding the pathogenesis of OLP and early-stage diagnosis and the design of direct and effective targeted therapy for OLP.

Interaction between altered miRNAs and target genes showed a dense interconnected molecular network in which multiple genes were predicated to be targeted by the same miRNA. However, differentially expressed miRNAs are usually analyzed independently, which may not reflect their involvement accurately. Few studies have analyzed how expression of miRNA and mRNA is integrated into a complex regulatory network, which may help elucidate the molecular mechanisms underlying the pathogenesis of OLP. Therefore, it is important to investigate disease-related miRNAs and genes from a systemic perspective. Several studies have been conducted to identify potential miRNA−mRNA modules using expression data sets, indicating the important roles of the regulation network in OLP. Ma et al.[17] discussed the miRNAs involved in the regulation of primary cytokines in OLP, suggesting that the miRNA−mRNA−cytokines regulation pathway may be associated with the etiopathogenesis of OLP. Gassling et al.[18] linked miRNAs to their potential targets from patients with OLP to HC individuals and found several potential miRNA−mRNA pairs that are functionally related to premalignant as well as inflammatory events.

Next-generation sequencing (NGS) is an increasingly popular technology for genome-wide analysis of transcripts and small RNA sequence and abundance. As such, it offers unparalleled opportunities to address health issues and improve our understanding of molecular mechanisms, thus contributing to the application of targeted therapy for OLP. In this study, using both types of expression data, OLP-associated miRNA−mRNA networks were initially identified; this could help identify the functional relationships between miRNAs and mRNAs, and such modules may unravel key mechanisms involved in OLP regulation. Therefore, the aim of the present study was to analyze candidate miRNAs and genes and screen out candidate pairs of miRNA−mRNA interactions; this can serve as a starting point for the study of basic molecular mechanisms and the development of new diagnostic and therapeutic approaches for patients with OLP by using NGS.

MATERIALS AND METHODS

Sample collection

Biopsy specimens of the buccal mucosa were collected from patients who had been clinically and pathologically diagnosed with reticular OLP according to the 2003 World Health Organization diagnostic criteria[19] at the Department of Oral Mucosal Diseases of the Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China). The patients did not have systemic disorders (e.g., cardiovascular disease and diabetes mellitus) or any soft tissue lesions in the oral mucosa. Smokers and those with severe alcoholism were excluded. Patients who had received immunotherapy or any medical treatment for OLP (local or systematic) within 3 months or had taken medication affecting RNA synthesis and transcription within 6 months of the study were also excluded (Table I displays the case groups). A sample of the buccal mucosa from reticular OLP lesions was obtained under sterile conditions and divided into 2 parts for pathologic examination and NGS. Normal mucosal tissues with no clinically visible inflammation were collected from retained wisdom teeth extractions and used as HCs. Signed informed consent forms were obtained before biopsy and pathologic examination. All experimental procedures were approved by the Research Ethics Committee of Shanghai Ninth People's Hospital (Approval number NSFC81400512) in compliance with the Helsinki Declaration.

Table I. Main clinical features of patients with oral lichen planus (OLP) and healthy controls (HCs)

Samples	*Sex*	*Age (y)*	*Duration (y)*	*Type*
OLP1	Male	43	13	Reticular
OLP2	Female	36	6	Reticular
OLP3	Female	53	4	Reticular
OLP4	Male	55	5	Reticular
OLP5	Female	59	1	Reticular
OLP6	Female	52	8	Reticular
OLP7	Female	42	10	Reticular
OLP8	Female	54	15	Reticular
OLP9	Male	44	2	Reticular
HC1	Male	37	–	–
HC2	Female	28	–	–
HC3	Male	44	–	–
HC4	Female	21	–	–

RNA extraction

Oral biopsy specimens were collected from lesions of patients diagnosed with OLP (n = 9) and compared with those from HCs (n = 4). Samples were suspended in RNA later (Qiagen, Valencia, CA) and immediately transferred to liquid nitrogen until RNA extraction. As the starting material, RNA was extracted from each tissue sample by grinding the tissues in a mortar under liquid nitrogen to prevent RNA degradation. Total RNA, including miRNA, was isolated using Trizol (Invitrogen, Carlsbad, CA) according to the manufacturer's protocol

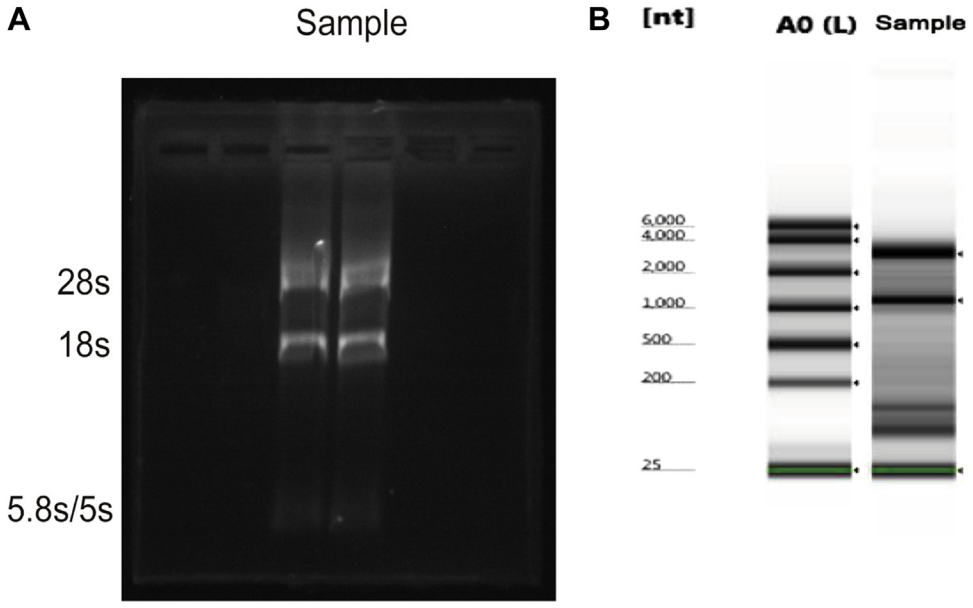

Fig. 1. RNA quality in RNase-containing gels. **A**, The presence of 28S, 18S, and 5.8S/5S ribosomal RNA (rRNA) bands occurred and were intact in gel with concentrations of 1.2%. **B**, RNA integrity number (RIN) value was assessed by using an Agilent 2200 TapeStation.

and quantified by using a bioanalyzer. Total RNA concentrations were 303 to 1000 ng/μL (40 μL). Small RNA samples for the NGS platform typically require at least 1 μg of total RNA as a starting input.

Denaturing gel electrophoresis

RNA samples were subjected to denaturing gel electrophoresis to visually assess the quality of RNA. A total of 1 μg of total mRNA per sample was mixed with an equal volume of ×2 RNA loading dye. The RNA samples were denatured by incubation at 70°C for 10 minutes and placed on ice for at least 2 minutes before electrophoresis. After denaturing, RNA was resolved by 1.5% denaturing gel electrophoresis (×10 3-(N-morpholino) propanesulfonic acid [MOPS] buffer, agarose, RNase-free water, and 37% formaldehyde). The gel was incubated in ×1 MOPS gel buffer for 10 minutes, followed by exposure to 100 V for 30 minutes. The quality of the prepared total RNA was assessed by using an Agilent 2200 TapeStation (Agilent Technologies, Palo Alto, CA). RNA integrity number values of 6.7 to 7.2; 28S/18S ribosomal RNA (rRNA) ratios of 1.2 to 1.3; and total RNA concentrations of 700 to 1000 ng/μL (30 μL) were obtained. Only samples containing suitable standards (m ≥10 μg; c ≥200 ng/μL; OD 260/280 ≥1.8; A260:A230 ≥2.0) were used for further analysis.[20] Finally, 4 RNA samples, including 2 OLP and 2 HC samples, qualified for the NGS platform and were selected for analysis. Samples were stored at −80°C until further use.

Next-generation sequencing

Qualifying total RNA was used for separate small RNA sequencing and transcriptome sequencing, which were performed by Ribobio Co. Ltd (Guangzhou, China) according to the manufacturer's instructions. RNA purity was assessed by using the ND-1000 Nanodrop. Briefly, for RNA sequencing, mRNA was enriched and separated into short fragments (200-700 bp). RNAs were ligated with a 3′ RNA adapter, followed by 5′ adapter ligation. Subsequently, the adapter-ligated RNAs were subjected to reverse transcriptase polymerase chain reaction (RT-PCR) and amplified with a low-cycle. The PCR products were selected for size by polyacrylamide gel electrophoresis according to the instructions of the TruSeq Small RNA Sample Prep Kit (Illumina, Inc., San Diego, CA). The purified library products were sequenced by using an Illumina HiSeq 2000.The primary sequencing data (raw reads) produced by the Illumina HiSeq 2000 were subjected to quality control. Following quality control, the raw reads were filtered and yielded clean reads that were aligned against the reference sequences by using the Short Oligonucleotide Analysis Package 2 tool.[21] Reads per kilobase of transcript per million mapped reads (RPKM) values[22] were used to compare gene

Table II. Number of reads matched to small RNA sequencing

Sample name	*HC1*	*HC2*	*OLP1*	*OLP2*
Mapping_Reads	18840285 (98.422%)	21506752 (98.4826%)	18601777 (98.7097%)	19642574 (98.7307%)

expressions in different samples. The expression fold change for each gene was calculated as the $\log_2$ ratio of the RPKM values. Subsequently, a strict algorithm was used to identify differentially expressed genes.[23] The *P* values for all genes were corrected for multiple tests by using a false discovery rate adjustment.[24]

For miRNA sequencing, total RNA from each sample was ligated with a 5′ adapter as well as a 3′ adapter for reverse transcription and then amplified and purified for sequencing. The small RNAs obtained from HiSeq deep sequencing covered almost every type of RNA. The small RNAs were annotated by comparing the present sequences with those in databases and by identifying overlaps in genome location. The same pipeline was used for both mRNA differential expression analysis and miRNA expression analysis.

Differential expression analysis

To determine the differential expression of miRNAs/mRNAs, the abundance of miRNAs/mRNAs in 4 libraries was normalized to values for comparison between 2 libraries and calculated in the form of $\log_2$ (fold changes). The fold-change and *P* value were calculated from the normalized expression using the following formula:

$$p(x/y) = \left(\frac{N_2}{N_1}\right)\frac{(x+y)!}{x!y!\left(1+\frac{N_2}{N_1}\right)^{(X+Y+1)}}$$

$$C(Y\le Y_{\min}/x)=\sum_{y=0}^{Y\le Y_{\min}} p(y/x)$$

$$D(Y\ge Y_{\max}/x)=\sum_{Y\ge Y_{\max}}^{\infty} p(y/x)$$

N1 and *x* represent the total count of clean reads and normalized expression levels of a given miRNA/mRNA in the RNA library of OLP tissue samples, respectively. *N2* and *y* represent the total count of clean reads and normalized expression levels of a given miRNA/mRNA in the small RNA library of HC tissue samples, respectively.

miRNA target prediction, Kyoto Encyclopedia of Genes and Genomes pathway analysis, and Gene Ontology term enrichment

To understand the molecular function of the 94 most abundant differentially expressed miRNAs in OLP tissue, the target genes of miRNAs were predicted using at least 3 of 5 analysis databases: Targetscan (http://www.targetscan.org), RNA22 (http://cbcsrv.watson.ibm.com/rna22.html), PicTar5 (http://pictar.mdc-berlin.de/), PITA (http://genie.weizmann.ac.il/pubs/mir07/), miRanda (http://www.microrna.org/microrna/home.do), and starBase v2.0 (http://starbase.sysu.edu.cn).The Database for Annotation, Visualization, and Integrated Discovery bioinformatics resources[25] was used to classify genes according to Kyoto Encyclopedia of Genes and Genomes (KEGG) functional annotations to identify pathways that were actively regulated by mRNAs in OLP tissue. In addition, Gene Ontology (GO) term enrichment of the target genes was calculated by using the GO: TermFinderPerl module in the Term Enrichment tool[26] under the setting conditions ($|\log_2$ [fold changes]$|>1$) and $Q < 0.05$).

Statistical analysis

Raw data of mRNA and miRNA expression profiles were processed by using the DESeq and edgeR software algorithms,[27,28] respectively. Fisher's exact test and hypergeometric distribution were used for statistical analyses of KEGG and GO data, respectively. $|\log_2$(fold changes)$|>1$ and a *P* value $< .05$ were set as the thresholds for significant differential expression. The *P* value was adjusted by using the Q value.

RESULTS

Analysis of RNA quality

In the assessment of the quality of RNA by using gel electrophoresis, the presence of 3 distinct bands suggests high-quality RNA. For eukaryotic RNA, the top band represents 28S rRNA, which runs at approximately 4.8 kb; the middle band represents 18S rRNA at approximately 2.0 kb; and the third band represents 5.8S (154 nt) and 5S (117 nt) RNA. Transfer RNAs (73-93 nt) may or may not be visible[29-32] (Figure 1A). Smeared bands indicate poor RNA quality. RNA integrity number value was up to 7.2 (Figure 1B). The results shown in Figure 1 indicate that we obtained high-quality RNA based on the criteria used.

Overall quality of the RNA sequencing data set

NGS was used to analyze miRNA and mRNA expression profiles in samples from patients with OLP compared with HCs, and 18,601,777 to 21,506,752 clean small RNA reads were obtained by small RNA library Illumina sequencing (2 OLP libraries and 2 HCs) (Table II). In addition, an average of 15 million reads were detected in each mRNA library, and 89.27%, 85.26%, 86.57%, and 86.59% clean reads were individually mapped to reference genomes in the HC1, HC2, OLP1, and OLP2 libraries, respectively (Table III). The high-quality small miRNA and mRNA sequencing data were used for further analysis.

miRNA and mRNA expression profiling in OLP

In the present study, a total of 390 miRNAs and 599 genes were detected and found to be coexpressed in patients with OLP and HCs. An overview of these differentially expressed miRNAs (DEMs) and differentially expressed genes (DEGs) is shown in supplementary Tables S1 and S2.The expression profile of miRNAs with >2-fold expression change in patients with OLP versus HCs is shown in Tables IV and V. Of the 390 miRNAs profiled, 94 were significant DEMs (>2-fold difference) between patients with OLP and HCs (51 upregulated and 43 downregulated). Furthermore, 35 of 94 DEMs showed highly significant changes, including 15 upregulated (see Table IV) and 20 downregulated (see Table V) miRNAs. The mRNAs in patients with OLP and HCs were quantified by sequencing total RNAs. RPKM values were calculated, and genes with low expression levels (RPKM <0.5) were removed.

Analysis of the identified miRNAs in OLP in previous studies

To evaluate published data of miRNAs in patients with OLP, we searched the literature for studies published before March 2017 by using the following PubMed terms: "microRNAs" and "oral lichen planus." The search yielded 20 reports that discussed "microRNAs in OLP." All 20 articles were included in the analysis, as shown in Table VI. Of the 94 DEMs mentioned in Tables IV and V, 24 were previously reported as showing the same expression trend using quantitative RT-PCR (qRT-PCR) tests or microarray technology or both, consistent with the present study. These results obtained by miRNA sequencing and qRT-PCR support the findings of the present study.

miRNA–mRNA interaction network based on NGS in OLP

A predicted miRNA target gene was defined as one showing an expression pattern opposite to that of the

Table III. Number of reads matched to messenger RNA (mRNA) sequencing

Samples	*Effective reads*	*Total mapped reads*	*Uniquely mapped reads*	*Multiple mapped reads*	*Reads map to '+'*	*Reads map to '−'*	*Unmapped reads*
HC1	14,206,277 (100%)	13,656,891 (96.13%)	12,682,154 (89.27%)	974,737 (6.86%)	6,715,653 (47.27%)	6,941,238 (48.86%)	549386 (3.87%)
HC2	14,910,141 (100%)	14,038,244 (94.15%)	12,712,054 (85.26%)	1,326,190 (8.89%)	6,917,153 (46.39%)	7,121,091 (47.76%)	871897 (5.85%)
OLP1	13,949,033 (100%)	13,267,005 (95.11%)	12,075,608 (86.57%)	1,191,397 (8.54%)	6,536,008 (46.86%)	6,730,997 (48.25%)	682028 (4.89%)
OLP2	15,208,340 (100%)	14,537,255 (95.59%)	13,169,173 (86.59%)	1,368,082 (9.00%)	7,156,127 (47.05%)	7,381,128 (48.53%)	671085 (4.41%)

Note: '+' indicates plus strand, '−' indicates minus strand.

Table IV. Much more significant differentially expressed micro-RNAs (DEMs) of upregulation in patients with oral lichen planus (OLP) compared with healthy controls (HCs)

miRNA_ID	*Control*	*OLP*	*|log2(foldchange)| (OLP1/Normal1)*	P *value*	*Significance label*
hsa-miR-133 a-3 p↑	13.54	155.69	3.52	.00	*
hsa-miR-155-5 p↑	117.63	634.86	2.43	.00	*
hsa-miR-1-3 p↑	123.90	1046.11	3.08	.01	*
hsa-miR-4521↑	5.22	60.91	3.54	.00	*
hsa-miR-335-5 p↑	10.45	57.65	2.46	.01	*
hsa-miR-150-5 p↑	271.10	2451.69	3.18	.02	*
hsa-miR-146 b-5 p↑	368.97	2768.89	2.91	.00	*
hsa-miR-100-5 p↑	1539.42	17630.05	3.52	.01	*
hsa-miR-411-5 p↑	18.13	255.93	3.82	.00	*
hsa-miR-142-5 p↑	104.74	709.10	2.76	.00	*
hsa-miR-31-5 p↑	161.11	498.41	1.63	.01	*
hsa-miR-423-3 p↑	145.65	464.24	1.67	.01	*
hsa-miR-1307-3 p↑	21.26	107.26	2.33	.00	*
hsa-miR-3184-5 p↑	43.10	176.17	2.03	.00	*
hsa-miR-4483↑	0.84	19.15	4.52	.00	*
hsa-miR-146 b-3 p↑	4.76	32.86	2.79	.03	†
hsa-miR-206↑	3.12	42.85	3.78	.03	†
hsa-miR-340-3 p↑	3.84	29.10	2.92	.01	†
hsa-miR-504-5 p↑	3.43	22.40	2.71	.02	†
hsa-miR-142-3 p↑	103.54	449.53	2.00	.02	†
hsa-miR-26 b-5 p↑	505.40	3892.02	2.92	.02	†
hsa-miR-27 a-3 p↑	2026.32	15462.42	2.93	.02	†
hsa-miR-146 a-5 p↑	820.61	7082.12	3.11	.02	†
hsa-miR-218-5 p↑	19.46	270.20	3.61	.01	†
hsa-miR-941↑	6.89	61.77	3.21	.03	†
hsa-miR-499 a-5 p↑	5.23	44.36	3.48	.02	†
hsa-miR-874-3 p↑	7.21	46.86	2.70	.02	†
hsa-miR-27 a-5 p↑	30.04	79.77	1.41	.03	†
hsa-miR-7-5 p↑	46.55	115.51	1.31	.04	†
hsa-miR-143-3 p↑	10315.20	24663.23	1.26	.03	†
hsa-miR-185-5 p↑	132.74	313.54	1.24	.04	†
hsa-miR-135 b-5 p↑	10.81	30.86	1.51	.05	†
hsa-miR-484↑	48.90	125.26	1.36	.03	†
hsa-miR-511-5 p↑	2.40	14.53	2.60	.02	†
hsa-miR-629-5 p↑	14.26	44.53	1.64	.02	†
hsa-miR-3182↑	11.39	36.94	1.70	.03	†
hsa-miR-548 ar-3 p↑	0.00	6.58	16.01	.03	†
hsa-miR-30 c-5 p↑	203.77	1615.77	2.99	.04	†
hsa-miR-139-5 p↑	25.37	277.42	3.45	.01	†
hsa-miR-128-3 p↑	29.86	281.93	3.24	.03	†
hsa-miR-125 a-5 p↑	391.24	3883.49	3.31	.01	†
hsa-miR-126-3 p↑	2533.92	20679.20	3.03	.04	†
hsa-miR-148 b-3 p↑	91.77	874.13	3.25	.02	†
hsa-miR-660-5 p↑	16.99	193.85	3.51	.02	†
hsa-miR-509-3-5 p↑	0.00	16.40	17.32	.04	†
hsa-let-7 e-5 p↑	16.21	106.91	2.72	.04	†
hsa-miR-203 a-3 p↑	4225.64	25365.36	2.59	.03	†
hsa-miR-144-5 p↑	25.96	186.88	2.85	.02	†
hsa-miR-126-5 p↑	72.03	444.83	2.63	.03	†
hsa-miR-374 a-5 p↑	44.56	260.72	2.55	.05	†
hsa-miR-335-3 p↑	2.84	39.31	3.79	.01	†

*$|\log_2(\text{Fold Change})| \geq 1$ and P value $< .01$.
†$|\log_2(\text{Fold Change})| \geq 1$ and P value $< .05$.

miRNA, reflecting the fact that mRNA expression was negatively correlated with miRNA expression. The predicted target mRNAs were found to be well matched on the basis of the databases used (>2 software programs from PITA, Targetscan, RNA22, picTar, and miRanda), and they were overlapped to DEGs in mRNA sequencing. On the basis of the complex interactions between miRNAs and mRNAs, altered

Table V. Much more significant differentially expressed micro-RNAs (DEMs) of downregulation in patients with oral lichen planus (OLP) compared with healthy controls (HCs)

miRNA_ID	*Control*	*OLP*	*|log2(foldchange)| (OLP1/Normal1)*	P *value*	*Significance label*
hsa-miR-4492↓	44.51	15.24	1.55	.00	*
hsa-miR-4532↓	19.97	7.18	1.48	.01	*
hsa-miR-3960↓	24.18	10.67	1.18	.00	*
hsa-miR-96-5 p↓	89.96	30.03	1.58	.00	*
hsa-miR-182-5 p↓	673.90	239.64	1.49	.00	*
hsa-miR-152-3 p↓	2261.74	510.78	2.15	.00	*
hsa-miR-195-5 p↓	505.06	115.41	2.13	.00	*
hsa-miR-141-3 p↓	363.75	146.30	1.31	.01	*
hsa-miR-3195↓	12.23	4.67	1.39	.01	*
hsa-miR-3196↓	12.59	3.71	1.76	.00	*
hsa-miR-3656↓	13.37	5.15	1.38	.00	*
hsa-miR-5787↓	6.78	1.70	2.00	.01	*
hsa-miR-7977↓	43.64	18.63	1.23	.00	*
hsa-miR-148 a-5 p↓	42.63	15.23	1.49	.00	*
hsa-miR-187-3 p↓	11.26	1.46	2.95	.01	*
hsa-miR-134-5 p↓	33.24	16.08	1.05	.01	*
hsa-miR-4497↓	160.77	60.17	1.42	.00	*
hsa-miR-4508↓	33.70	16.18	1.06	.01	*
hsa-miR-944↓	64.67	6.10	3.41	.00	*
hsa-miR-7975↓	55.58	17.14	1.70	.01	*
hsa-miR-23 a-3 p↓	2709.96	1346.94	1.01	.02	†
hsa-miR-4516↓	6.00	2.45	1.29	.03	†
hsa-miR-23 b-3 p↓	1667.73	828.81	1.01	.02	†
hsa-miR-202-5 p↓	11.99	3.16	1.93	.02	†
hsa-miR-138-5 p↓	5.51	2.32	1.25	.05	†
hsa-miR-183-5 p↓	311.09	138.71	1.17	.01	†
hsa-miR-204-5 p↓	81.96	36.51	1.17	.02	†
hsa-miR-205-5 p↓	16947.73	8111.26	1.06	.01	†
hsa-miR-365 a-3 p↓	110.80	46.91	1.24	.01	†
hsa-miR-493-5 p↓	48.90	19.21	1.35	.01	†
hsa-miR-193 b-3 p↓	103.96	46.22	1.17	.02	†
hsa-miR-656-3 p↓	10.66	1.54	2.79	.01	†
hsa-miR-664 a-3 p↓	23.61	8.91	1.41	.03	†
hsa-miR-6510-3 p↓	50.62	25.10	1.01	.04	†
hsa-miR-99 a-5 p↓	4951.07	1752.85	1.50	.05	†
hsa-miR-199 a-5 p↓	4066.48	1265.34	1.68	.02	†
hsa-miR-27 b-3 p↓	16182.20	5272.86	1.62	.03	†
hsa-miR-148 a-3 p↓	11111.71	3696.29	1.59	.03	†
hsa-miR-127-3 p↓	593.40	161.40	1.88	.01	†
hsa-miR-136-3 p↓	76.38	21.86	1.80	.03	†
hsa-miR-376 c-3 p↓	24.61	5.63	2.13	.05	†
hsa-miR-497-5 p↓	85.78	21.26	2.01	.02	†
hsa-miR-455-5 p↓	279.43	95.20	1.55	.04	†

*$|\log_2(\text{Fold Change})| \geq 1$ and P value $< .01$.
†$|\log_2(\text{Fold Change})| \geq 1$ and P value $< .05$.

miRNAs and their predicted-target mRNAs were identified, as listed in Table VII. Table VIII shows the altered mRNAs and their corresponding miRNAs. Tables IV to VI show that the upregulated mRNAs (ATF3, GREM1, CCR7, and ACTA1) and the downregulated miRNAs (hsa-miR-135a, hsa-miR-128, hsa-miR-218, hsa-miR-125a, and hsa-let-7e) were well matched. The consistent results obtained by sequencing associated mRNAs and miRNAs validate our analyses and strengthen our conclusion.

KEGG analysis of DEGs between patients with OLP and HCs

After mapping to the reference canonical pathways, the 599 DEGs between patients with OLP and HCs were assigned to 218 pathways. According to the enriched gene numbers and $\log_{10}$ (P value), 30 significantly enriched pathways were identified and sorted from 218 KEGG pathways, including 4 classifications: cellular processes (3 terms), human diseases (18 terms), metabolism (6 terms), and organismal systems (3 terms)

Table VI. Summary of identified micro-RNAs (miRNAs) in oral lichen planus (OLP) in evaluating studies

miRNA-ID	*NGS*	*qRT-PCR tests*	*Microarray analysis*
hsa-miR-155	Increased	Increased[12*]	Increased[16]
hsa-miR-203	Increased	Increased[12]	
hsa-miR-146a	Increased	Increased[12]	Increased[13]
hsa-miR-342	Increased		Increased[12,14]
hsa-miR-143	Increased		Increased[12,15]
hsa-miR-132	Increased		Increased[12,14]
hsa-miR-31	Increased		Increased[13]
hsa-miR-335	Increased		Increased[12]
hsa-miR-146b	Increased		Increased[14]
hsa-miR-26b	Increased		Increased[14]
hsa-miR-133a	Increased		Increased[13]
hsa-miR-206	Increased		Increased[13]
hsa-miR-27a	Increased		Increased[15]
hsa-miR-135	Increased		Increased[12]
hsa-miR-30c	Increased		Increased[13,15]
hsa-miR-484	Increased		Increased[16]
hsa-miR-27b	Decreased	Decreased[13]	
hsa-miR-202	Decreased		Decreased[16]
hsa-miR-204	Decreased		Decreased[13]
hsa-miR-148a	Decreased		Decreased[12]
hsa-miR-205	Decreased		Decreased[12,13]
hsa-miR-23b	Decreased		Decreased[12,13,15]
hsa-miR-99a	Decreased		Decreased[12]
hsa-miR-152	Decreased		Decreased[13]

*References.

(Figure 2); "osteoclast differentiation," "metabolic pathways" plus "primary immunodeficiency," "tuberculosis," and "phagosome" were significantly enriched in each classification, respectively. The human diseases category contained the largest pathway numbers (18) among the 4 classifications, whereas the pathway "primary immunodeficiency," which contained 11 genes, showed the highest gene expression levels in the human diseases category. This indicates that remarkable gene expression changes may occur in $\geq$1 of these genes. The KEGG analysis in the present study contributes to our understanding of the etiology and pathogenesis of OLP and could be subjected to further analysis.

GO enrichment annotation analysis of all detected genes between patients with OLP and HCs

In the present study, 599 detected DEGs had at least 1 GO annotation. All matched relevant genes were classified into 3 functional categories: molecular functions, biologic processes, and cellular components, including 30 terms (Figure 3). These genes were enriched in the top 10 terms in the 3 functional categories. The terms "extracellular region," "cell periphery," and "plasma membrane," which included 165, 218, and 212 genes, respectively, were relatively more dominant in the cellular component category. In the molecular function category, the term "protein binding" was the most significantly enriched and dominant, with 305 genes. There was also relatively uniform enrichment for the terms "immune response," "immune system process," and "response to stimulus," indicating the activation of immune pathways in patients with OLP compared with HCs. Therefore, further exploration of additional mechanisms relevant to immune activities in OLP is warranted.

DISCUSSION

The etiology of OLP and its potential to represent a premalignant phenotype remain poorly understood.[8,33] However, miRNAs were shown to be of value as biomarkers to predict the risk of oral premalignant lesions.[34] The abundance of data generated from gene expression and miRNA analyses could improve our understanding of the pathogenesis of OLP. Several studies have examined the mechanisms of gene expression in OLP. The combination of genome-wide miRNA profiling and genome-wide mRNA profiling is a powerful tool for the identification of regulatory networks, as demonstrated in previous studies.[35-37] In the present study, we compared the expression of 390 miRNAs and 599 mRNAs in oral biopsy specimens from patients with OLP and HCs by using NGS. The aim of the present study was to identify, catalog, and quantify the expression of all known miRNAs and mRNAs. It is hoped that improving our understanding of this pathologic issue will facilitate future discoveries of the etiology and pathogenesis of OLP.

NGS provides unprecedented opportunities to examine intergeneric regulation with the data obtained from 2 pivotal components, namely, miRNAs and mRNAs. In the present study, we detected 94 DEMs and 599 DEGs between patients with OLP and HCs. Further evaluation of studies analyzing patients with OLP[17,18,38-40] showed that 4 (hsa-miR-155, hsa-miR-203, hsa-miR-146 a, and hsa-miR-27 b) of 24 miRNAs showing alterations in previous studies and in the present study had been validated by qRT-PCR tests in large sample data of patients with OLP. Arão TC et al. reported that the expression of miRNA-146a and miRNA-155 in OLP affects immune regulation and may contribute to T helper 1 cell differentiation in response to an as-yet-undetermined antigen.[41] Shen et al. showed that miR-203 was highly abundant in keratinocytes and upregulated in OLP lesions, targeting the immunosuppressive gene *IL22*.[42] Zhang et al. indicated that the downregulation of miR-27 b in epithelial keratinocytes of OLP may be part of a specific inflammatory response in activated cytotoxic T cells that triggers apoptosis of epithelial cells.[38] Aberrant expression of miRNAs has been associated

Table VII. The predicted target messenger RNAs (mRNAs) that match differentially expressed genes (DEGs) are regulated by changed micro-RNAs (miRNAs)

miRNA	*Predicted target mRNAs that match DEGs*
hsa-miR-133 a-3 p↑	COL1 A1↓
hsa-miR-27 a-3 p↑	CSRP2↓,NFE2 L2↓
hsa-miR-218-5 p↑	COL1 A1↓
hsa-miR-143-3 p↑	KLF5↓
hsa-miR-100-5 p↑	FGFR3↓
hsa-miR-30 c-5 p↑	PITX1↓
hsa-miR-128-3 p↑	COL3 A1↓
hsa-miR-148 b-3 p↑	KLF5↓
hsa-let-7 e-5 p↑	ARL4 D↓,COL1 A1↓,COL3 A1↓
hsa-miR-203 a-3 p↑	SPARC↓
hsa-miR-374 a-5 p↑	PITX2↓
hsa-miR-23 b-3 p↓	TRIB1↑,ADRA2 A↑,MARCKSL1↑,TNFAIP3↑,PTGER4↑
hsa-miR-138-5 p↓	SH2 B3↑,LENG8↑,RARA↑
hsa-miR-96-5 p↓	MSN↑,CSRNP1↑,GPC3↑,TTYH3↑,TSC22 D3↑,RGS2↑,LCP1↑,CBX6↑
hsa-miR-182-5 p↓	TNS1↑,MYADM↑,PTHLH↑,GPC3↑,THBS1↑
hsa-miR-141-3 p↓	LENG8↑,KLF6↑,WIPF1↑,SIK1↑,KCTD12↑,THBS1↑
hsa-miR-23 a-3 p↓	MARCKSL1↑,TRIB1↑,ADRA2 A↑,TNFAIP3↑,PTGER4↑
hsa-miR-183-5 p↓	EGR1↑
hsa-miR-204-5 p↓	DNAJB1↑,FAM107 B↑
hsa-miR-205-5 p↓	ACSL1↑,RARA↑,CSF1↑,ACTB↑
hsa-miR-365 a-3 p↓	EFEMP1↑,ARRB2↑
hsa-miR-193 b-3 p↓	IGFBP5↑,MCL1↑,ETS1↑
hsa-miR-152-3 p↓	KLF6↑,TNFRSF1 B↑,SIK1↑,CSF1↑,SERPINE1↑,PBXIP1↑
hsa-miR-195-5 p↓	ACSL1↑,LITAF↑,MYADM↑,RNF213↑,TSC22 D3↑,PTHLH↑,SNCG↑,ZYX↑
hsa-miR-99 a-5 p↓	TRIB1↑
hsa-miR-199 a-5 p↓	CTGF↑,PIK3 CD↑
hsa-miR-27 b-3 p↓	LITAF↑,CSRNP1↑,CSF1↑,RND3↑,GREM1↑,RARA↑,PPIF↑
hsa-miR-148 a-3 p↓	KLF6↑,TGOLN2↑,TNFRSF1 B↑,SIK1↑,CSF1↑,SERPINE1↑,PBXIP1↑
hsa-miR-497-5 p↓	ACSL1↑,LITAF↑,MYADM↑,TSC22 D3↑,PTHLH↑,SNCG↑,ZYX↑
hsa-miR-455-5 p↓	ETS1↑,MAN1 A1↑,SOCS3↑

Table VIII. The changed messenger RNAs (mRNAs) are regulated by micro-RNAs (miRNAs)

mRNAs	*miRNAs that are predicted to act on target mRNAs by >2 of Targetscan, picTar, RNA22, PITA, and miRanda/mirSVR, and then overlapped to changed miRNAs*
ACTA1↑	hsa-miR-4500↓, hsa-miR-495-3 p↓, hsa-let-7 e-5 p↓, hsa-let-7 g-5 p↓, hsa-let-7 d-5 p↓
CIDEC↑	hsa-miR-29 b-3 p↓
PCOLCE2↑	hsa-miR-92 b-3 p↓
ATF3↑	hsa-miR-135 b-5 p↓, hsa-miR-135 a-5 p↓, hsa-miR-494-3 p↓, hsa-miR-7-5 p↓
GREM1↑	hsa-miR-128-3 p↓, hsa-miR-218-5 p↓
PDLIM3↑	hsa-miR-137↓
TAGAP↑	hsa-miR-92 b-3 p↓
RGS1↑	hsa-miR-29 b-3 p↓, hsa-miR-223-3 p↓
CCR7↑	hsa-miR-125 b-5 p↓, hsa-miR-4500↓, hsa-let-7 e-5 p↓, hsa-miR-125 a-5 p↓, hsa-let-7 g-5 p↓, hsa-let-7 d-5 p↓

with OLP, suggesting their involvement in the etiopathogenesis of this disease.

Selecting both OLP-associated miRNAs and mRNAs to create a functional link was shown to be a valid experimental setup: miRNAs involved in certain biologic process control the biologic process-associated transcripts. The present approach allowed the identification of miRNA−mRNA interaction networks based on NGS. The regulation of miRNA-coding genes can be involved in any type of pathophysiologic process and/or pathway. On the one hand, in a review of miRNA−mRNA interaction networks in OLP, DEGs including ATF3, GREM1, CCR7, and ACTA1 and DEMs including hsa-miR-135a, hsa-miR-128, hsa-miR-218, hsa-miR-125a, and hsa-let-7e were identified as important factors that merit further analysis. On the other hand, chronic inflammation is one of the main characteristics of OLP lesions, and certain genes that are induced in response to injury and inflammatory stimuli are overexpressed in OLP.[43,44] In line with the results of the present GO analysis, many inflammation-related terms, such as "chemokine activity," "cytokine

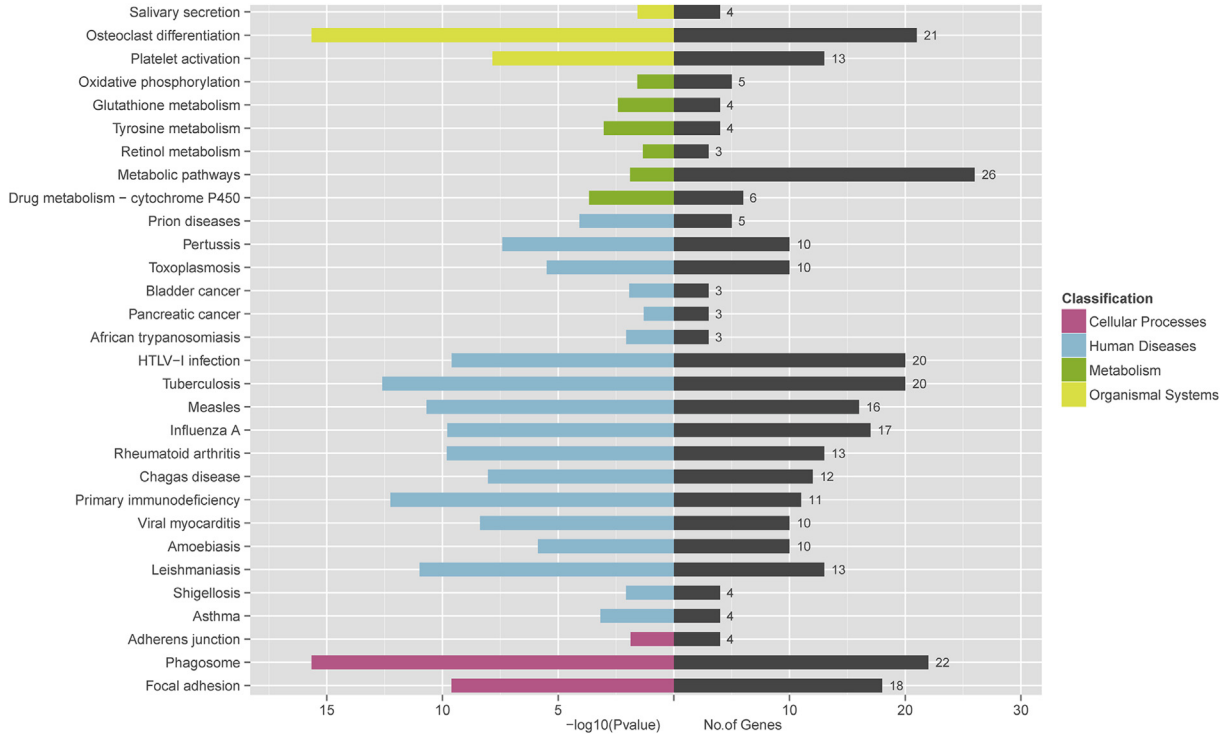

Fig. 2. Functional annotation of different express genes between patients with oral lichen planus (OLP) and healthy controls (HCs) based on Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. The 599 differentially expressed genes (DEGs) retrieved from next-generation sequencing (NGS) results between patients with OLP and HCs were classified according to KEGG functional annotations to identify pathways that were significantly active in OLP tissue. The top 4 over-represented pathways are phagosome (cellular processes); tuberculosis and primary immunodeficiency (human diseases); and osteoclast differentiation (organismal systems), respectively.

binding," "cytokine activity," "response to stimulus," and "defense response" are significantly enriched in 3 functional categories. Similarly, autoimmunity has been suggested as a possible cause of OLP, and previous studies detected autoantibodies against p63[45] and T-cell responses.[46] Consistent with these observations, we showed that DEGs were significantly enriched in immune-related terms (8 of 10), which dominated the molecular functions derived from the GO data and "primary immunodeficiency" pathway in the KEGG data in OLP. The present results support previous data indicating the complex etiology of OLP. In addition to highly conserved factors, other significant GO terms (such as "protein binding" in molecular function and "extracellular region part" in cellular component) and KEGG pathways (such as "phagosome" in cellular processes, "tuberculosis" in human diseases, "metabolic pathways" in metabolism, and "osteoclast differentiation" in organismal systems) are poorly conserved.

The studies reported in the literature have demonstrated that multiple mechanisms may contribute to the altered expression of 5 miRNAs in multiple disorders, especially in inflammatory events. For instance, miR-135a, an inflammation-related miRNA, was reported as an early specific biomarker to predict the probability of a chlamydial genital infection leading to pelvic inflammatory disease.[47] miR-128 has indicated the prominent role played by neuronal miRNAs in the inflammatory response of hepatic stellate cells during fibrosis by interacting with mRNA members of the chemokine signaling network.[48] Elucidation of the molecular mechanism reveals that the secretory protein Slit2 represses inflammatory responses by inhibiting the Pyk2-NF-κB pathway via targeting of miR-218.[49] Kanaan et al.[50] examined the tumorigenic effect of differentially expressed Let-7e on the TP53 pathway in inflammatory bowel disease. De la Rica et al.[51] described the direct involvement of NF-κB in shutting down some anti-inflammatory activities through an miR-99b/let-7e/125a cluster-dependent mechanism in inflammatory monocytic differentiation processes. Although the 5 miRNAs are not yet reported in OLP, the regulatory mechanism by miRNAs, the conservative small molecule, are prevalent in biologic processes; similarly, it is likely that all the 5 miRNA biomarkers may participate in OLP initiation and progression. Interestingly, it has become more evident that they may play an important role in the pathogenesis of OLP. Hu et al.[16] showed that downregulated miR-125a in patients with OLP increased CCl5/CCR5, which is

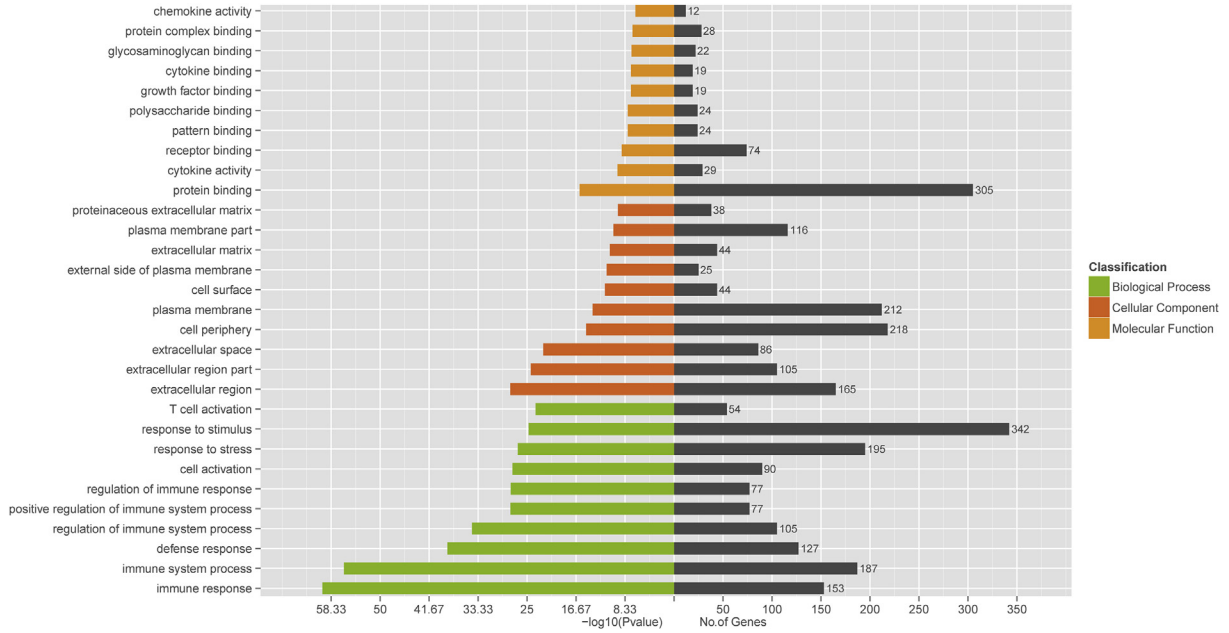

Fig. 3. Functional annotation of different express genes between patients with oral lichen planus (OLP) and healthy controls (HCs) based on Gene Ontology (GO) terms. There are 3 ontologies in GO: molecular functions, cellular components, and biologic processes. GO categories were assigned to all 599 differentially expressed genes (DEGs); intriguingly, the top 4 over-represented GO terms are immune response and immune system process (biological process); extracellular region (cellular component); and protein binding (molecular function), respectively.

involved in local immune disorders and the persistent inflammation, suggesting that highly expressed miR-125a was highly related to the severity of OLP.

Taken together, the genome-wide mapping of a regulatory miRNA−mRNA network that controls disease-associated processes in OLP presents a starting point for further studies, which may lead to future breakthroughs in therapy. Assessing the direct interaction of miRNAs and their suggested targets is one of the next steps required to broaden our understanding of OLP.

The present study has some limitations, including the small samples for the NGS platform. The relative result of a single miRNA or mRNA need to be validated by using other methods or with a larger number of study patients. It would be interesting to see the impact of the 5 miRNAs candidates in larger cohorts of patients. However, there is no denying that NGS can reveal the global pattern of DEMs and DEGs, and further investigation of the remaining DEMs in the present study is necessary.

CONCLUSIONS

The potential premalignant transformation to OLP underscores the importance of understanding the pathogenesis of OLP. Here, we provided an atlas of miRNA and mRNA expression in patients with OLP and HCs by using NGS. The preliminary analysis of mRNA−miRNA networks provides clues to elucidate gene expression mechanisms in the development and progression of OLP. These data will, it is hoped, serve as a reference point for future functional studies or as the basis for experiments aimed at revealing the role of miRNAs and mRNAs in OLP. However, our investigation is just an initial step, and further studies are required to determine the potential roles of miRNAs and mRNAs as candidate biomarkers of pathogenesis for OLP.

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Reprint requests:

Guoyao Tang, PhD
Department of Oral Mucosal Disease
No.500, Quxi Road
Huangpu District
Shanghai 200011
Tanggy@shsmu.edu.cn

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.oooo.2017.05.513.

SUPPLEMENTARY DATA

Table S1. Differentially expressed miRNAs in OLP compared to HC

miRNA_ID	*Control*	*olp*	*|log2(foldchange)|*	P *value*	*Significance label*
hsa-let-7d-5p	86.5372	177.726	1.038262406	.394233229	
hsa-let-7e-5p	16.2102	106.9108	2.7215	.041842087	*
hsa-let-7f-1-3p	2.99515	6.00425	1.003355792	.847310405	
hsa-let-7g-5p	2972.17315	7099.6399	1.256227686	.24340788	
hsa-miR-100-5p	1539.4189	17630.0516	3.5175	.005265285	**
hsa-miR-101-5p	1.0648	2.38365	1.162589939	1	
hsa-miR-103a-3p	1167.3922	2418.269	1.0506854	.438931965	
hsa-miR-10a-3p	0.4963	3.7967	2.935461648	.17695442	
hsa-miR-10b-3p	5.0531	12.22515	1.274611531	.537811914	
hsa-miR-1180-3p	4.83835	11.3019	1.223978288	.612950502	
hsa-miR-1185-5p	0.4963	0	12.27699674	1	
hsa-miR-1226-3p	0	0.8546	13.0610336	1	
hsa-miR-1227-3p	0	0.2653	11.37340896	1	
hsa-miR-124-3p	0.2612	0	11.35093918	1	
hsa-miR-1254	0	0.85315	13.0585837	1	
hsa-miR-1255a	0	1.1967	13.54677391	.517847983	
hsa-miR-125a-5p	391.2426	3883.4859	3.3112	.012806375	*
hsa-miR-125b-5p	1857.9634	4147.38145	1.158478661	.398515518	
hsa-miR-1260a	0	0.27645	11.43280286	1	
hsa-miR-126-3p	2533.9189	20679.2014	3.0287	.035968624	*
hsa-miR-126-5p	72.03	444.8335	2.6266	.032462184	*
hsa-miR-1268a	0.25185	1.4312	2.506588656	1	
hsa-miR-1273c	0	0.2653	11.37340896	1	
hsa-miR-1273h-3p	0.22895	1.49135	2.703514409	1	
hsa-miR-1273h-5p	0	0.2653	11.37340896	1	
hsa-miR-127-3p	593.3969	161.3967	1.8784	.012500181	*
hsa-miR-1275	0	1.64355	14.00452773	.518593947	
hsa-miR-1277-3p	0	1.2037	13.55518825	.517865652	
hsa-miR-1278	1.29345	2.89605	1.162862225	1	
hsa-miR-128-1-5p	0	0.2653	11.37340896	1	
hsa-miR-128-3p	29.8561	281.9327	3.2392	.026692415	*
hsa-miR-1285-5p	0	0.377	11.88034881	1	
hsa-miR-1287-5p	2.47625	6.23765	1.332845629	.68934216	
hsa-miR-1292-5p	0	0.37145	11.85895231	1	
hsa-miR-1293	0	1.56245	13.9315224	.277985813	
hsa-miR-1295a	1.0619	0.37145	1.515407982	.277196917	
hsa-miR-129-5p	0	0.45235	12.14322376	1	
hsa-miR-1299	3.33855	1.4634	1.189897483	.177637496	
hsa-miR-1301-3p	1.8068	5.7125	1.660685441	.525609737	
hsa-miR-1304-3p	1.04545	2.20065	1.073805647	1	
hsa-miR-1306-3p	0	0.27645	11.43280286	1	
hsa-miR-1306-5p	0.53915	2.0973	1.959774626	1	
hsa-miR-1307-3p	21.2618	107.2627	2.3348	.001107603	**
hsa-miR-132-3p	7.2456	21.6375	1.578356752	.226593716	
hsa-miR-132-5p	5.2095	18.171	1.802421001	.179764235	
hsa-miR-133a-3p	13.5409	155.68895	3.523271017	.004530966	**
hsa-miR-133a-5p	0.44405	5.78535	3.703610203	.083601452	
hsa-miR-133b	0	0.76945	12.90961187	1	
hsa-miR-1343-3p	0	0.29185	11.51101135	1	
hsa-miR-134-5p	33.2446	16.0844	1.0474	.007783264	**
hsa-miR-135a-5p	7.20565	18.1731	1.334604056	.333937739	
hsa-miR-135b-5p	10.8137	30.8619	1.513	.049529827	*
hsa-miR-136-3p	76.3752	21.8647	1.8045	.031435647	*
hsa-miR-137	0.31345	0	11.61401961	1	
hsa-miR-138-5p	5.5104	2.31525	1.250989064	.046271691	*
hsa-miR-139-3p	2.9832	8.14645	1.449310807	.622051113	
hsa-miR-139-5p	25.3685	277.4222	3.4509	.012784528	*

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Table S1. Continued

miRNA_ID	*Control*	*olp*	*|log2(foldchange)|*	P *value*	*Significance label*
hsa-miR-1-3p	123.896	1046.1071	3.077829046	.006681257	**
hsa-miR-141-3p	363.7488	146.2993	1.314	.006085512	**
hsa-miR-142-3p	103.5402	449.5322	1.9953	.01531575	*
hsa-miR-142-5p	104.7417	709.1034	2.7592	.00181154	**
hsa-miR-143-3p	10315.2009	24663.2284	1.2576	.032067265	*
hsa-miR-143-5p	69.3708	174.7253	1.332688096	.229179467	
hsa-miR-144-5p	25.9638	186.8803	2.8476	.021592189	*
hsa-miR-145-3p	37.41605	103.0052	1.460988004	.139699266	
hsa-miR-145-5p	411.51895	958.7165	1.220145395	.257404473	
hsa-miR-1468-5p	0	0.61025	12.57518467	1	
hsa-miR-146a-3p	0.8594	7.4329	3.112523516	.129193197	
hsa-miR-146a-5p	820.61335	7082.1189	3.11	.015770339	*
hsa-miR-146b-3p	4.75515	32.8609	2.788809237	.030091797	*
hsa-miR-146b-5p	368.9733	2768.88935	2.907719075	.002391497	**
hsa-miR-147a	0.84295	1.7523	1.055730826	1	
hsa-miR-148a-3p	11111.7078	3696.29	1.5879	.033446872	*
hsa-miR-148a-5p	42.6319	15.2299	1.4851	.001080015	**
hsa-miR-148b-3p	91.7662	874.1345	3.2518	.01838835	*
hsa-miR-150-3p	0.8923	4.865	2.44683906	.430504041	
hsa-miR-150-5p	271.0975	2451.6946	3.184	1.80E-02	**
hsa-miR-151a-3p	405.72205	872.1238	1.104041232	.523132931	
hsa-miR-152-3p	2261.7412	510.7794	2.1466	.003699279	**
hsa-miR-155-5p	117.63	634.85715	2.432175958	.001652451	**
hsa-miR-16-1-3p	18.78365	59.29835	1.65851453	.083762711	
hsa-miR-16-2-3p	1.94	5.9918	1.626932817	.371591568	
hsa-miR-181b-3p	0	0.29185	11.51101135	1	
hsa-miR-182-5p	673.8991	239.6401	1.4917	.002661605	**
hsa-miR-1827	0.57465	1.33635	1.217542478	1	
hsa-miR-183-3p	0	0.3267	11.67375074	1	
hsa-miR-183-5p	311.0906	138.7111	1.1653	.01136849	*
hsa-miR-185-3p	1.3757	5.165	1.908602454	.482716567	
hsa-miR-185-5p	132.7424	313.5448	1.24	.039226922	*
hsa-miR-187-3p	11.2647	1.4576	2.9501	.005479339	**
hsa-miR-188-5p	0.5882	1.74965	1.572687665	1	
hsa-miR-18a-3p	1.4637	4.38445	1.582775988	.621820425	
hsa-miR-190b	0.653	1.47315	1.17374944	1	
hsa-miR-191-3p	0.2873	0.59345	1.046568491	1	
hsa-miR-191-5p	737.17945	1649.2228	1.161698552	.465998218	
hsa-miR-192-3p	0	0.5166	12.33483193	1	
hsa-miR-192-5p	89.78685	224.7554	1.323779707	.368273547	
hsa-miR-193b-3p	103.9581	46.2193	1.1695	.015388465	*
hsa-miR-195-3p	7.5155	16.4146	1.1270386	.635549859	
hsa-miR-195-5p	505.0586	115.4054	2.1297	.004831892	**
hsa-miR-196a-5p	0.6269	2.29285	1.870834741	.654398492	
hsa-miR-196b-5p	0.3657	2.2775	2.638718522	.654218956	
hsa-miR-1976	0.62075	1.3014	1.067980197	1	
hsa-miR-199a-5p	4066.4847	1265.3377	1.6843	.02370747	*
hsa-miR-202-5p	11.9943	3.15735	1.925562862	.018476335	*
hsa-miR-203a-3p	4225.6404	25365.3616	2.5856	.030176207	*
hsa-miR-204-5p	81.9649	36.5085	1.1667	.016485348	*
hsa-miR-205-3p	1.2873	0.4775	1.430775669	.651653069	
hsa-miR-205-5p	16947.7261	8111.2554	1.0631	.014306084	*
hsa-miR-206	3.1206	42.85385	3.779529473	.030381303	*
hsa-miR-210-5p	0.8104	1.8012	1.152252304	1	
hsa-miR-211-5p	3.6014	20.48165	2.507702193	.066387718	
hsa-miR-2116-3p	0	0.6996	12.77231457	1	
hsa-miR-212-3p	0.68945	2.0763	1.590497076	1	
hsa-miR-212-5p	0.47015	3.0413	2.693495111	.273819976	
hsa-miR-215-5p	0.60075	1.7217	1.518997132	.653190468	
hsa-miR-217	0	0.7233	12.82037844	1	
hsa-miR-218-5p	19.4614	270.20365	3.61125	.012131388	*

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Table S1. Continued

miRNA_ID	*Control*	*olp*	*|log2(foldchange)|*	P *value*	*Significance label*
hsa-miR-219a-1-3p	0.2612	0	11.35093918	1	
hsa-miR-219a-5p	0.2612	0	11.35093918	1	
hsa-miR-222-3p	288.27195	634.30515	1.137746592	.372455728	
hsa-miR-222-5p	0	0.27645	11.43280286	1	
hsa-miR-223-3p	66.4499	172.26825	1.374317896	.260694376	
hsa-miR-223-5p	4.06705	12.11765	1.575055309	.360701394	
hsa-miR-2277-5p	0.4963	1.54155	1.635097324	1	
hsa-miR-23a-3p	2709.9624	1346.9409	1.0086	.017954515	*
hsa-miR-23a-5p	0.2612	1.18685	2.18391081	1	
hsa-miR-23b-3p	1667.73255	828.80925	1.008775936	.018307986	*
hsa-miR-24-2-5p	44.07745	143.04735	1.698380104	.139264353	
hsa-miR-25-5p	1.0687	2.36535	1.146196751	1	
hsa-miR-26b-5p	505.4009	3892.0172	2.92095	.022269046	*
hsa-miR-27a-3p	2026.32	15462.42105	2.9297	.024795568	*
hsa-miR-27a-5p	30.0381	79.7684	1.409	.034451952	*
hsa-miR-27b-3p	16182.1977	5272.8604	1.6177	.029980393	*
hsa-miR-28-3p	127.9802	259.5205	1.019927878	.659960826	
hsa-miR-28-5p	24.4679	54.89785	1.165859364	.470784475	
hsa-miR-29a-5p	0	0.2653	11.37340896	1	
hsa-miR-29b-1-5p	0	0.6423	12.64903158	1	
hsa-miR-29b-2-5p	2.78355	5.62595	1.015170733	1	
hsa-miR-29b-3p	123.8724	253.9117	1.035472098	.97546473	
hsa-miR-301a-3p	0.2612	0.68985	1.401127802	1	
hsa-miR-301a-5p	0.5224	2.51065	2.26483412	.423520544	
hsa-miR-301b-3p	0	0.4245	12.05154884	1	
hsa-miR-3065-3p	0.33955	1.72025	2.340922306	.65339901	
hsa-miR-3074-3p	1.306	4.43765	1.764640989	.255583656	
hsa-miR-30a-3p	67.76295	174.24925	1.362583859	.190786629	
hsa-miR-30c-1-3p	1.9829	3.98515	1.007022105	1	
hsa-miR-30c-2-3p	5.9793	13.1828	1.140608326	.749280311	
hsa-miR-30c-5p	203.7722	1615.7666	2.9872	.044173566	*
hsa-miR-30e-3p	15.8279	37.50695	1.244688095	.392827719	
hsa-miR-3135b	33.92415	87.4083	1.365457612	.485840761	
hsa-miR-3155b	0	0.3184	11.63662462	1	
hsa-miR-31-5p	161.1089	498.4146	1.6293	.008834594	**
hsa-miR-3173-5p	0	0.29185	11.51101135	1	
hsa-miR-3182	11.3884	36.9438	1.6978	.032386763	*
hsa-miR-3184-3p	60.38615	136.12975	1.17269279	.437847943	
hsa-miR-3184-5p	43.0982	176.1742	2.0313	.00223283	**
hsa-miR-3194-3p	0	0.53065	12.3735449	1	
hsa-miR-3195	12.2263	4.6697	1.3886	.005837072	**
hsa-miR-3196	12.5927	3.7145	1.7613	.001743679	**
hsa-miR-32-3p	0.8097	3.27865	2.017642518	.512540338	
hsa-miR-328-3p	19.86655	54.06495	1.444352248	.346902985	
hsa-miR-330-3p	6.8561	17.628	1.362408745	.666958958	
hsa-miR-330-5p	3.2615	8.5986	1.398566155	.647559478	
hsa-miR-331-5p	1.3592	2.8024	1.043905136	1	
hsa-miR-335-3p	2.8391	39.3062	3.7913	.013538161	*
hsa-miR-335-5p	10.45195	57.653	2.463623553	.006915268	**
hsa-miR-338-3p	4.5272	9.90445	1.129457821	.681660086	
hsa-miR-338-5p	5.0135	13.99435	1.480954452	.289031149	
hsa-miR-339-3p	18.00075	38.22335	1.086397208	1	
hsa-miR-339-5p	37.33225	85.37175	1.193336291	.437444213	
hsa-miR-340-3p	3.8381	29.1024	2.922673927	.013454662	*
hsa-miR-340-5p	113.14045	241.0332	1.091117063	.323629456	
hsa-miR-342-3p	84.23815	243.5206	1.531498161	.333249167	
hsa-miR-342-5p	2.3273	9.0626	1.961267816	.426216697	
hsa-miR-346	0	0.53065	12.3735449	1	
hsa-miR-34a-3p	0.2612	0.7219	1.466644107	1	
hsa-miR-34b-3p	0	1.07655	13.39412771	.517587998	
hsa-miR-34b-5p	4.60005	15.22	1.726246911	.234422788	

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Table S1. Continued

miRNA_ID	*Control*	*olp*	*|log2(foldchange)|*	P *value*	*Significance label*
hsa-miR-34c-3p	0.31345	1.29025	2.041343396	1	
hsa-miR-34c-5p	10.935	31.69425	1.535267909	.263020008	
hsa-miR-3529-3p	70.69235	152.72445	1.111305038	.428095737	
hsa-miR-361-3p	141.365	455.69375	1.68863961	.137913784	
hsa-miR-3614-5p	0	0.42725	12.06086478	1	
hsa-miR-3615	13.32295	31.10045	1.223021892	.480575148	
hsa-miR-3622a-5p	0	0.37145	11.85895231	1	
hsa-miR-3653-5p	0	0.53065	12.3735449	1	
hsa-miR-3656	13.3711	5.1473	1.3772	.004550577	**
hsa-miR-3659	0	0.27645	11.43280286	1	
hsa-miR-365a-3p	110.8015	46.9092	1.24	.012009678	*
hsa-miR-365b-5p	0.31345	1.24275	1.987228868	1	
hsa-miR-3690	0	0.3184	11.63662462	1	
hsa-miR-369-5p	2.95575	6.77665	1.197048011	.713664738	
hsa-miR-370-5p	0	0.37145	11.85895231	1	
hsa-miR-374a-5p	44.5551	260.7177	2.5488	.047339727	*
hsa-miR-374c-3p	0	0.6423	12.64903158	1	
hsa-miR-375	65.5562	227.49725	1.795044971	.123249701	
hsa-miR-376a-3p	7.24145	3.23815	1.161108789	.099757736	
hsa-miR-376c-3p	24.6052	5.6295	2.1279	.048036813	*
hsa-miR-378a-5p	8.87155	19.8326	1.16061573	.758776716	
hsa-miR-379-3p	1.959	4.0634	1.052569992	.795392752	
hsa-miR-3909	1.2286	4.06905	1.72767672	.574974502	
hsa-miR-3910	1.4634	0.4245	1.785487705	.277532578	
hsa-miR-3928-3p	0.2873	0.8867	1.625888083	1	
hsa-miR-3940-3p	0	0.77635	12.92249149	1	
hsa-miR-3960	24.1779	10.66935	1.1808	.003973839	**
hsa-miR-411-5p	18.1334	255.931	3.819	.004044811	**
hsa-miR-412-5p	0.4179	0.9816	1.23197749	1	
hsa-miR-423-3p	145.6458	464.2353	1.6724	.007458592	**
hsa-miR-423-5p	22.03105	59.8367	1.441492357	.448309941	
hsa-miR-424-3p	1.18895	5.7042	2.262336521	.319038738	
hsa-miR-4306	0	1.07935	13.39787514	.517557335	
hsa-miR-4324	0.70525	1.82785	1.373941017	.654232027	
hsa-miR-4423-5p	0	0.3016	11.55842071	1	
hsa-miR-4433a-3p	0.2873	1.7538	2.609854337	.653384988	
hsa-miR-4443	0	0.2513	11.29519496	1	
hsa-miR-4473	0.653	1.43275	1.133631999	1	
hsa-miR-4483	0.8358	19.1505	4.518	.001743679	**
hsa-miR-4485-3p	1.01285	0.4775	1.084847893	.651342719	
hsa-miR-4492	44.5093	15.24215	1.5525	.000691118	**
hsa-miR-4497	160.774	60.1656	1.418	.000452933	**
hsa-miR-449a	0.2612	0	11.35093918	1	
hsa-miR-449c-5p	0	1.03185	13.33294564	.517603965	
hsa-miR-4500	26.3508	66.5177	1.335891523	.395755224	
hsa-miR-4508	33.7026	16.1849	1.0582	.00694389	**
hsa-miR-4516	6.00385	2.45475	1.29031183	.02557965	*
hsa-miR-4521	5.22405	60.9103	3.5434456	.00038029	**
hsa-miR-4524a-3p	0	0.29185	11.51101135	1	
hsa-miR-4532	19.9651	7.18405	1.48065	.006135751	**
hsa-miR-454-5p	0.4963	1.8292	1.881928465	.653561144	
hsa-miR-455-5p	279.433	95.1994	1.5535	.044576368	*
hsa-miR-4634	0.27475	0	11.42390377	1	
hsa-miR-4645-3p	0	0.398	11.95855272	1	
hsa-miR-4662a-5p	0	0.2653	11.37340896	1	
hsa-miR-4677-3p	0.47015	1.40055	1.574800466	1	
hsa-miR-4705	0	0.6633	12.69544581	1	
hsa-miR-4742-3p	0	0.377	11.88034881	1	
hsa-miR-4746-5p	0	0.398	11.95855272	1	
hsa-miR-4772-3p	0	0.74985	12.87238631	1	
hsa-miR-4772-5p	0	0.4776	12.22158712	1	

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Table S1. Continued

miRNA_ID	*Control*	*olp*	*|log2(foldchange)|*	P *value*	*Significance label*
hsa-miR-4787-5p	0.89295	0	13.12436368	.278972796	
hsa-miR-483-3p	3.11735	6.44705	1.04831903	1	
hsa-miR-484	48.8969	125.2571	1.357	.033037515	*
hsa-miR-486-5p	238.7846	477.57555	1.000019183	.775310256	
hsa-miR-488-3p	0	0.62	12.5980525	1	
hsa-miR-489-3p	0	0.7275	12.82873153	1	
hsa-miR-491-5p	0	0.53065	12.3735449	1	
hsa-miR-493-5p	48.8969	19.2094	1.348	.013892852	*
hsa-miR-494-3p	12.69925	27.19385	1.098537121	.490439809	
hsa-miR-495-3p	5.76835	12.74035	1.143174302	.556035321	
hsa-miR-497-5p	85.7785	21.2615	2.0123	.017208672	*
hsa-miR-499a-5p	5.22565	44.3621	3.4809	.024875082	*
hsa-miR-5000-3p	0	0.29185	11.51101135	1	
hsa-miR-5001-3p	0	0.6479	12.66155544	1	
hsa-miR-500a-3p	21.0639	50.30955	1.256059708	.429366875	
hsa-miR-500b-5p	0.44405	1.1995	1.433639119	1	
hsa-miR-501-3p	3.1857	10.9819	1.785445361	.295645428	
hsa-miR-501-5p	1.04545	2.45755	1.233096704	1	
hsa-miR-502-3p	9.58065	24.46855	1.352733166	.387342742	
hsa-miR-502-5p	0.47015	1.1492	1.289436875	1	
hsa-miR-503-5p	2.3592	5.47215	1.21381005	.690065109	
hsa-miR-504-5p	3.4256	22.4038	2.709314848	.019534722	*
hsa-miR-505-3p	7.7677	17.87355	1.202266819	.523042051	
hsa-miR-505-5p	0	1.12265	13.4546206	.517500673	
hsa-miR-506-3p	0	0.5572	12.44397954	1	
hsa-miR-508-3p	0.2873	1.1409	1.989542447	1	
hsa-miR-509-3-5p	0	16.397	17.3231	.039970491	*
hsa-miR-509-3p	0.2873	0.95515	1.733169324	1	
hsa-miR-5095	0.98645	0.4245	1.216481373	.517259116	
hsa-miR-509-5p	0.8097	2.3614	1.544183059	1	
hsa-miR-511-3p	1.88805	5.3117	1.492276696	.657380843	
hsa-miR-511-5p	2.4031	14.5262	2.5957	.022208097	*
hsa-miR-514a-5p	0	0.53065	12.3735449	1	
hsa-miR-5193	0	0.398	11.95855272	1	
hsa-miR-532-3p	10.39845	21.063	1.018342439	.825939506	
hsa-miR-532-5p	92.54855	268.21535	1.535109513	.174784069	
hsa-miR-539-5p	0	0.37145	11.85895231	1	
hsa-miR-543	2.56045	11.22255	2.131931232	.126221353	
hsa-miR-548a-5p	0.31345	0.82805	1.401482555	1	
hsa-miR-548ac	0	0.27645	11.43280286	1	
hsa-miR-548ak	0	0.2653	11.37340896	1	
hsa-miR-548ao-3p	0	1.5654	13.93424373	.519167897	
hsa-miR-548ap-3p	0.31345	0	11.61401961	1	
hsa-miR-548ar-3p	0	6.5845	16.0068	.034782609	*
hsa-miR-548as-5p	0	0.35185	11.7807448	1	
hsa-miR-548av-3p	2.42695	5.06615	1.061745407	1	
hsa-miR-548h-5p	0	0.9299	13.18285986	.518319729	
hsa-miR-548o-3p	1.25375	3.5635	1.507045224	.513223851	
hsa-miR-548y	0	0.62	12.5980525	1	
hsa-miR-550a-3-5p	0.31345	0.7219	1.203563674	1	
hsa-miR-5699-5p	0	0.37145	11.85895231	1	
hsa-miR-570-3p	0	0.29185	11.51101135	1	
hsa-miR-5787	6.7771	1.6981	1.9968	.009223959	**
hsa-miR-585-3p	2.18185	5.8271	1.417226148	.658364049	
hsa-miR-589-5p	3.02605	8.1157	1.423279711	.623552574	
hsa-miR-605-3p	0	0.3449	11.75196241	1	
hsa-miR-6077	0.25185	1.30135	2.369372393	1	
hsa-miR-6134	0	0.4245	12.05154884	1	
hsa-miR-616-5p	0	0.29185	11.51101135	1	
hsa-miR-624-5p	0.57465	1.19385	1.054866151	1	
hsa-miR-625-5p	0.47015	1.25675	1.418504666	1	

(*continued on next page*)

Table S1. Continued

miRNA_ID	*Control*	*olp*	*|log2(foldchange)|*	P *value*	*Significance label*
hsa-miR-627-3p	0.4963	1.09475	1.14131709	1	
hsa-miR-629-5p	14.2616	44.5336	1.6427	.024760562	*
hsa-miR-642a-3p	0.22895	0.9021	1.978254804	1	
hsa-miR-642a-5p	0	1.41455	13.78805555	.517560415	
hsa-miR-6500-3p	0	0.6633	12.69544581	1	
hsa-miR-6503-3p	0.8794	4.72395	2.425402257	.430135705	
hsa-miR-6503-5p	0.29765	1.8041	2.599590509	.653350335	
hsa-miR-6504-5p	0	0.8029	12.9710046	1	
hsa-miR-6510-3p	50.6208	25.0996	1.0121	.039155241	*
hsa-miR-6511a-3p	0.4963	1.0403	1.067715271	1	
hsa-miR-6513-3p	0.31345	0.8225	1.391780349	1	
hsa-miR-652-5p	0.2873	1.89765	2.72358403	.653045142	
hsa-miR-653-3p	0	1.6128	13.97727992	.518678632	
hsa-miR-656-3p	10.657	1.5389	2.7918	.014145884	*
hsa-miR-659-3p	0	0.29185	11.51101135	1	
hsa-miR-660-5p	16.9886	193.8453	3.5123	.015057018	*
hsa-miR-663b	0.435	0	12.08679969	1	
hsa-miR-664a-3p	23.6126	8.9149	1.4053	.032308876	*
hsa-miR-671-3p	2.55205	5.15115	1.013237957	1	
hsa-miR-6720-3p	0	0.5837	12.51101135	1	
hsa-miR-6733-5p	0.2612	0	11.35093918	1	
hsa-miR-6747-3p	0	0.5962	12.54158066	1	
hsa-miR-676-3p	0.44405	1.01235	1.188914121	1	
hsa-miR-6774-3p	0	0.29185	11.51101135	1	
hsa-miR-6803-3p	0	0.37145	11.85895231	1	
hsa-miR-6806-3p	0	0.2653	11.37340896	1	
hsa-miR-6833-3p	0	0.6465	12.65843465	1	
hsa-miR-6842-3p	0.68625	2.3571	1.780206817	1	
hsa-miR-6866-5p	0	0.29185	11.51101135	1	
hsa-miR-6873-3p	0	0.2653	11.37340896	1	
hsa-miR-7-1-3p	2.6581	6.5071	1.291619344	.690144677	
hsa-miR-744-5p	32.78905	78.69895	1.263130284	.545868159	
hsa-miR-7-5p	46.5461	115.5059	1.3112	.041318299	*
hsa-miR-760	0	0.98725	13.26919975	.517272106	
hsa-miR-766-3p	1.80425	4.19185	1.216187838	1	
hsa-miR-7705	0	0.3016	11.55842071	1	
hsa-miR-7706	1.96675	4.23945	1.108063527	1	
hsa-miR-7973	0	0.2653	11.37340896	1	
hsa-miR-7975	55.5836	17.1399	1.6973	.005032071	**
hsa-miR-7976	0.33955	1.50525	2.14830718	1	
hsa-miR-7977	43.6393	18.6257	1.2284	.000552913	**
hsa-miR-874-3p	7.2092	46.8561	2.7004	.015527944	*
hsa-miR-874-5p	0.22895	0.79595	1.797645241	1	
hsa-miR-885-5p	0	0.6465	12.65843465	1	
hsa-miR-891a-5p	0	0.37145	11.85895231	1	
hsa-miR-92a-1-5p	0.61755	1.3516	1.130040401	1	
hsa-miR-92b-3p	23.6952	51.4138	1.117560808	.395166263	
hsa-miR-92b-5p	0.5224	1.7622	1.754150869	.652884676	
hsa-miR-9-3p	0.99255	2.4897	1.326760228	.721972342	
hsa-miR-941	6.8906	61.7673	3.20545	.027455329	*
hsa-miR-942-3p	0	0.27645	11.43280286	1	
hsa-miR-944	64.6734	6.1024	3.4057	1.62E-05	**
hsa-miR-95-5p	0	0.4245	12.05154884	1	
hsa-miR-96-5p	89.9577	30.0346	1.5826	.003901411	**
hsa-miR-99a-5p	4951.0687	1752.8451	1.498	.046141997	*

*| log2(Fold Change) | $\geq$1 and *P*-value<.05.
**| log2(Fold Change) | $\geq$ 1 and *P*-value<.01.

Table S2. Differentially expressed mRNAs in OLP compared to HC

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
S100A8	18571.70	7540.02	1.30	.00	0.00	S100 calcium binding protein A8
KRT13	13062.15	6097.29	1.10	.00	0.00	keratin 13
KRT76	1899.05	11.99	7.31	.00	0.00	keratin 76
KRT4	3184.28	553.13	2.53	.00	0.00	keratin 4
PI3	579.83	2774.70	2.26	.00	0.00	peptidase inhibitor 3, skin-derived
CD74	870.85	3164.92	1.86	.00	0.00	CD74 molecule, major histocompatibility complex, class II invariant chain
FDCSP	3169.83	0.00	14.21	.00	0.00	follicular dendritic cell secreted protein
FABP5	2719.68	893.51	1.61	.00	0.00	fatty acid binding protein 5 (psoriasis-associated)
KRT17	518.78	1528.50	1.56	.00	0.00	keratin 17
ACTB	1177.42	2450.09	1.06	.00	0.00	actin, beta
COL1A1	1482.87	382.59	1.95	.00	0.00	collagen, type I, alpha 1
SPRR2E	781.81	1613.20	1.05	.00	0.00	small proline-rich protein 2E
CST3	667.19	1427.89	1.10	.00	0.00	cystatin C
C1QC	99.30	521.08	2.39	.00	0.00	complement component 1, q subcomponent, C chain
SPRR2G	83.14	482.03	2.54	.00	0.00	small proline-rich protein 2G
KRT15	708.49	147.80	2.26	.00	0.00	keratin 15
APOE	236.69	751.33	1.67	.00	0.00	apolipoprotein E
SPRR2F	263.81	793.24	1.59	.00	0.00	small proline-rich protein 2F
KRT6B	706.11	1426.05	1.01	.00	0.00	keratin 6B
LCE3D	90.85	476.18	2.39	.00	0.00	late cornified envelope 3D
LYZ	70.57	415.83	2.56	.00	0.00	lysozyme
C1QB	75.53	424.36	2.49	.00	0.00	complement component 1, q subcomponent, B chain
DEFB4A	17.99	282.63	3.97	.00	0.00	defensin, beta 4A
IFI27	427.92	977.91	1.19	.00	0.00	interferon, alpha-inducible protein 27
AQP3	1159.59	431.40	1.43	.00	0.00	aquaporin 3 (Gill blood group)
C1QA	88.21	416.12	2.24	.00	0.00	complement component 1, q subcomponent, A chain
RNASE1	173.01	541.44	1.65	.00	0.00	ribonuclease, RNase A family, 1 (pancreatic)
CCL18	12.18	223.79	4.20	.00	0.00	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)
SPARC	805.07	263.74	1.61	.00	0.00	secreted protein, acidic, cysteine-rich (osteonectin)
IFI30	77.39	356.69	2.20	.00	0.00	interferon, gamma-inducible protein 30
CLEC3B	76.66	352.62	2.20	.00	0.00	C-type lectin domain family 3, member B
PLA2G2A	2.11	193.19	6.51	.00	0.00	phospholipase A2, group IIA (platelets, synovial fluid)
KRT1	880.84	322.42	1.45	.00	0.00	keratin 1
RPS4Y1	243.80	0.00	8.93	.00	0.00	ribosomal protein S4, Y-linked 1
SPRR2B	30.65	237.50	2.95	.00	0.00	small proline-rich protein 2B
COL1A2	988.63	401.71	1.30	.00	0.00	collagen, type I, alpha 2
MT1X	383.18	74.93	2.35	.00	0.00	metallothionein 1X
KRT3	240.07	19.82	3.60	.00	0.00	keratin 3
COL3A1	929.55	371.73	1.32	.00	0.00	collagen, type III, alpha 1
CTSZ	116.08	393.82	1.76	.00	0.00	cathepsin Z
RHCG	1040.75	460.26	1.18	.00	0.00	Rh family, C glycoprotein
ACTA1	0.00	171.07	7.96	.00	0.00	actin, alpha 1, skeletal muscle
IGJ	56.32	260.35	2.21	.00	0.00	immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides
DNAJB1	214.74	506.91	1.24	.00	0.00	DnaJ (Hsp40) homolog, subfamily B, member 1
CRIP1	164.54	432.08	1.39	.00	0.00	cysteine-rich protein 1 (intestinal)
MIR650	845.10	360.84	1.23	.00	0.00	microRNA 650
TXN	856.49	373.48	1.20	.00	0.00	thioredoxin
DPT	39.94	211.71	2.41	.00	0.00	dermatopontin
CXCL9	2.51	115.75	5.52	.00	0.00	chemokine (C-X-C motif) ligand 9
LCE3E	27.75	168.82	2.61	.00	0.00	late cornified envelope 3E
WFDC12	3.08	109.35	5.15	.00	0.00	WAP four-disulfide core domain 12
GSN	252.78	516.91	1.03	.00	0.00	gelsolin
HLA-DQB1	21.05	150.62	2.84	.00	0.00	major histocompatibility complex, class II, DQ beta 1
LCN2	91.41	278.22	1.61	.00	0.00	lipocalin 2
C3	20.38	146.02	2.84	.00	0.00	complement component 3
CXCL10	2.53	103.25	5.35	.00	0.00	chemokine (C-X-C motif) ligand 10
TACSTD2	448.55	157.00	1.51	.00	0.00	tumor-associated calcium signal transducer 2
DES	1.53	103.17	6.07	.00	0.00	desmin

(*continued on next page*)

Table S2. Continued

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
LAPTM5	53.80	212.14	1.98	.00	0.00	lysosomal protein transmembrane 5
IL32	62.83	223.51	1.83	.00	0.00	interleukin 32
MFAP4	103.49	288.80	1.48	.00	0.00	microfibrillar-associated protein 4
DAPL1	171.64	24.06	2.83	.00	0.00	death associated protein-like 1
TYROBP	60.04	216.19	1.85	.00	0.00	TYRO protein tyrosine kinase binding protein
BST2	57.95	210.98	1.86	.00	0.00	bone marrow stromal cell antigen 2
IGFBP5	215.87	444.98	1.04	.00	0.00	insulin-like growth factor binding protein 5
HLA-DQA1	33.99	164.36	2.27	.00	0.00	major histocompatibility complex, class II, DQ alpha 1
MIR205HG	196.33	38.70	2.34	.00	0.00	MIR205 host gene (non-protein coding)
DOK2	10.23	100.55	3.30	.00	0.00	docking protein 2, 56kDa
CLU	73.41	219.18	1.58	.00	0.00	clusterin
ARHGDIB	89.17	242.83	1.45	.00	0.00	Rho GDP dissociation inhibitor (GDI) beta
NR4A1	7.52	92.73	3.62	.00	0.00	nuclear receptor subfamily 4, group A, member 1
HLA-DRB3	13.44	106.27	2.98	.00	0.00	major histocompatibility complex, class II, DR beta 3
KLK5	29.52	139.12	2.24	.00	0.00	kallikrein-related peptidase 5
HSPH1	77.31	221.24	1.52	.00	0.00	heat shock 105kDa/110kDa protein 1
G0S2	8.27	91.26	3.46	.00	0.00	G0/G1switch 2
F13A1	36.45	147.54	2.02	.00	0.00	coagulation factor XIII, A1 polypeptide
LCP1	23.39	119.82	2.36	.00	0.00	lymphocyte cytosolic protein 1 (L-plastin)
IFI6	62.25	188.26	1.60	.00	0.00	interferon, alpha-inducible protein 6
COTL1	56.80	178.76	1.65	.00	0.00	coactosin-like 1 (Dictyostelium)
CORO1A	40.34	149.79	1.89	.00	0.00	coronin, actin binding protein, 1A
KRT19	219.98	62.07	1.83	.00	0.00	keratin 19
PERP	535.36	249.81	1.10	.00	0.00	PERP, TP53 apoptosis effector
CD9	543.46	257.47	1.08	.00	0.00	CD9 molecule
CXCL13	85.93	5.40	3.99	.00	0.00	chemokine (C-X-C motif) ligand 13
SERPING1	85.88	219.75	1.36	.00	0.00	serpin peptidase inhibitor, clade G (C1 inhibitor), member 1
CD68	65.87	185.59	1.49	.00	0.00	CD68 molecule
MIR205	166.84	39.21	2.09	.00	0.00	microRNA 205
MYADM	20.13	105.63	2.39	.00	0.00	myeloid-associated differentiation marker
CD24	367.24	151.52	1.28	.00	0.00	CD24 molecule
CD14	37.74	136.59	1.86	.00	0.00	CD14 molecule
CCL19	129.05	273.97	1.09	.00	0.00	chemokine (C-C motif) ligand 19
SLURP1	92.54	221.55	1.26	.00	0.00	secreted LY6/PLAUR domain containing 1
MCL1	70.97	189.17	1.41	.00	0.00	myeloid cell leukemia sequence 1 (BCL2-related)
CBR1	298.32	112.49	1.41	.00	0.00	carbonyl reductase 1
ITGB2	20.08	102.19	2.35	.00	0.00	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)
JUND	105.25	237.89	1.18	.00	0.00	jun D proto-oncogene
SOD2	100.48	230.81	1.20	.00	0.00	superoxide dismutase 2, mitochondrial
LCE3A	18.19	97.51	2.42	.00	0.00	late cornified envelope 3A
CTGF	12.13	82.24	2.76	.00	0.00	connective tissue growth factor
ARPC1B	109.47	239.68	1.13	.00	0.00	actin related protein 2/3 complex, subunit 1B, 41kDa
SOD3	120.12	253.33	1.08	.00	0.00	superoxide dismutase 3, extracellular
CCL5	23.76	105.21	2.15	.00	0.00	chemokine (C-C motif) ligand 5
FOLR2	19.13	96.08	2.33	.00	0.00	folate receptor 2 (fetal)
TGFBI	27.06	111.27	2.04	.00	0.00	transforming growth factor, beta-induced, 68kDa
UCP2	17.37	91.54	2.40	.00	0.00	uncoupling protein 2 (mitochondrial, proton carrier)
LGMN	38.94	130.74	1.75	.00	0.00	legumain
PPP1R15A	23.11	100.66	2.12	.00	0.00	protein phosphatase 1, regulatory subunit 15A
TCAP	1.06	52.43	5.62	.00	0.00	titin-cap
CKM	0.00	57.82	7.61	.00	0.00	creatine kinase, muscle
HMOX1	22.33	98.59	2.14	.00	0.00	heme oxygenase (decycling) 1
ATF3	3.53	57.03	4.01	.00	0.00	activating transcription factor 3
SRGN	37.39	122.74	1.72	.00	0.00	serglycin
BAG3	101.36	216.98	1.10	.00	0.00	BCL2-associated athanogene 3
ISG15	36.91	120.02	1.70	.00	0.00	ISG15 ubiquitin-like modifier
PITX1	319.17	139.50	1.19	.00	0.00	paired-like homeodomain 1
WARS	18.57	86.49	2.22	.00	0.00	tryptophanyl-tRNA synthetase
DBI	263.15	105.66	1.32	.00	0.00	diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)
ADH1B	0.00	48.39	6.80	.00	0.00	alcohol dehydrogenase 1B (class I), beta polypeptide

(*continued on next page*)

Table S2. Continued

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
TNC	11.65	71.03	2.61	.00	0.00	tenascin C
SAMHD1	14.97	76.88	2.36	.00	0.00	SAM domain and HD domain 1
LGALS7	125.12	31.04	2.01	.00	0.00	lectin, galactoside-binding, soluble, 7
TNNT1	3.43	49.93	3.86	.00	0.00	troponin T type 1 (skeletal, slow)
RAC2	33.25	109.15	1.71	.00	0.00	ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)
CCL21	89.78	192.90	1.10	.00	0.00	chemokine (C-C motif) ligand 21
SPINT2	296.61	129.96	1.19	.00	0.00	serine peptidase inhibitor, Kunitz type, 2
FGL2	8.80	62.12	2.82	.00	0.00	fibrinogen-like 2
SERPINA3	3.87	50.12	3.70	.00	0.00	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3
PRDX5	347.26	163.44	1.09	.00	0.00	peroxiredoxin 5
FLNA	84.48	184.09	1.12	.00	0.00	filamin A, alpha
CD52	30.04	101.68	1.76	.00	0.00	CD52 molecule
TRIM29	372.68	181.08	1.04	.00	0.00	tripartite motif containing 29
MSN	78.35	174.10	1.15	.00	0.00	moesin
STAT1	17.42	78.35	2.17	.00	0.00	signal transducer and activator of transcription 1, 91kDa
CXCR4	13.73	71.04	2.37	.00	0.00	chemokine (C-X-C motif) receptor 4
CYR61	12.96	68.18	2.40	.00	0.00	cysteine-rich, angiogenic inducer, 61
FCER1G	31.29	100.99	1.69	.00	0.00	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide
CLEC10A	6.74	53.96	3.00	.00	0.00	C-type lectin domain family 10, member A
FOSB	10.16	60.75	2.58	.00	0.00	FBJ murine osteosarcoma viral oncogene homolog B
DNASE1L3	99.39	22.99	2.11	.00	0.00	deoxyribonuclease I-like 3
PTPRCAP	48.20	124.90	1.37	.00	0.00	protein tyrosine phosphatase, receptor type, C-associated protein
LTBP4	50.66	128.47	1.34	.00	0.00	latent transforming growth factor beta binding protein 4
TNNC1	1.47	38.97	4.73	.00	0.00	troponin C type 1 (slow)
IL36A	43.64	117.52	1.43	.00	0.00	interleukin 36, alpha
KRT24	51.57	0.00	8.91	.00	0.00	keratin 24
DSG1	216.92	88.61	1.29	.00	0.00	desmoglein 1
CSRP2	138.98	43.91	1.66	.00	0.00	cysteine and glycine-rich protein 2
UQCRH	274.17	125.03	1.13	.00	0.00	ubiquinol-cytochrome c reductase hinge protein
RPS24	329.67	161.31	1.03	.00	0.00	ribosomal protein S24
IGFBP6	71.89	157.11	1.13	.00	0.00	insulin-like growth factor binding protein 6
IL10RA	9.66	57.25	2.57	.00	0.00	interleukin 10 receptor, alpha
PLIN1	0.00	43.00	8.36	.00	0.00	perilipin 1
FXYD3	142.32	46.76	1.61	.00	0.00	FXYD domain containing ion transport regulator 3
MB	0.00	35.87	5.60	.00	0.00	myoglobin
IRF8	8.89	54.74	2.62	.00	0.00	interferon regulatory factor 8
LSP1	36.81	103.67	1.49	.00	0.00	lymphocyte-specific protein 1
HSPB6	7.24	50.35	2.80	.00	0.00	heat shock protein, alpha-crystallin-related, B6
ANXA6	27.84	88.69	1.67	.00	0.00	annexin A6
ODAM	38.85	0.00	6.28	.00	0.00	odontogenic, ameloblast asssociated
HCLS1	19.64	74.27	1.92	.00	0.00	hematopoietic cell-specific Lyn substrate 1
CD53	22.90	79.66	1.80	.00	0.00	CD53 molecule
CCL13	4.14	42.34	3.35	.00	0.00	chemokine (C-C motif) ligand 13
CD7	8.54	52.31	2.61	.00	0.00	CD7 molecule
ACP5	19.83	73.70	1.89	.00	0.00	acid phosphatase 5, tartrate resistant
MPEG1	10.68	56.30	2.40	.00	0.00	macrophage expressed 1
FILIP1L	8.07	50.71	2.65	.00	0.00	filamin A interacting protein 1-like
SLCO2B1	12.96	60.40	2.22	.00	0.00	solute carrier organic anion transporter family, member 2B1
WISP2	35.07	97.48	1.47	.00	0.00	WNT1 inducible signaling pathway protein 2
RGS1	5.11	43.21	3.08	.00	0.00	regulator of G-protein signaling 1
CSF1R	14.04	61.81	2.14	.00	0.00	colony stimulating factor 1 receptor
SNHG5	98.03	26.09	1.91	.00	0.00	small nucleolar RNA host gene 5 (non-protein coding)
LYVE1	2.61	36.75	3.82	.00	0.00	lymphatic vessel endothelial hyaluronan receptor 1
TMPRSS11A	67.77	12.26	2.47	.00	0.00	transmembrane protease, serine 11A
TMEM176B	41.28	105.89	1.36	.00	0.00	transmembrane protein 176B
PLIN4	0.00	31.93	6.19	.00	0.00	perilipin 4
SPI1	23.43	76.52	1.71	.00	0.00	spleen focus forming virus (SFFV) proviral integration oncogene spi1
KLF6	24.92	78.98	1.66	.00	0.00	Kruppel-like factor 6

(*continued on next page*)

Table S2. Continued

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
IER5	37.80	99.07	1.39	.00	0.00	immediate early response 5
CD3E	11.92	55.72	2.23	.00	0.00	CD3e molecule, epsilon (CD3-TCR complex)
EMP3	58.40	128.57	1.14	.00	0.00	epithelial membrane protein 3
DSP	262.07	126.38	1.05	.00	0.00	desmoplakin
FCGRT	66.99	140.07	1.06	.00	0.00	Fc fragment of IgG, receptor, transporter, alpha
CCL2	13.73	58.12	2.08	.00	0.00	chemokine (C-C motif) ligand 2
CTSS	14.38	58.89	2.03	.00	0.00	cathepsin S
TNFAIP3	7.73	45.69	2.56	.00	0.00	tumor necrosis factor, alpha-induced protein 3
NMU	56.50	9.09	2.64	.00	0.00	neuromedin U
PTGR1	74.92	17.20	2.12	.00	0.00	prostaglandin reductase 1
GPC3	1.36	30.41	4.48	.00	0.00	glypican 3
RGS2	8.62	46.86	2.44	.00	0.00	regulator of G-protein signaling 2, 24kDa
PGD	134.90	49.65	1.44	.00	0.00	phosphogluconate dehydrogenase
SELPLG	9.60	48.35	2.33	.00	0.00	selectin P ligand
CLCA4	54.40	8.82	2.62	.00	0.00	chloride channel accessory 4
SLC40A1	22.38	71.12	1.67	.00	0.00	solute carrier family 40 (iron-regulated transporter), member 1
THBS1	10.99	50.82	2.21	.00	0.00	thrombospondin 1
ALDH3A1	129.30	47.48	1.45	.00	0.00	aldehyde dehydrogenase 3 family, member A1
MYL2	0.00	36.16	9.25	.00	0.00	myosin, light chain 2, regulatory, cardiac, slow
CD163	9.47	47.16	2.32	.00	0.00	CD163 molecule
KLK12	129.57	47.82	1.44	.00	0.00	kallikrein-related peptidase 12
STAB1	14.78	56.94	1.95	.00	0.00	stabilin 1
GBP1	7.37	42.57	2.53	.00	0.00	guanylate binding protein 1, interferon-inducible
APOC1	6.27	40.08	2.68	.00	0.00	apolipoprotein C-I
GREM1	2.17	30.28	3.80	.00	0.00	gremlin 1, DAN family BMP antagonist
IRF1	11.67	50.93	2.13	.00	0.00	interferon regulatory factor 1
CD37	20.80	66.97	1.69	.00	0.00	CD37 molecule
KLK11	142.55	56.21	1.34	.00	0.00	kallikrein-related peptidase 11
GNLY	2.42	30.62	3.66	.00	0.00	granulysin
FAM26F	3.49	33.32	3.25	.00	0.00	family with sequence similarity 26, member F
CD4	12.69	52.47	2.05	.00	0.00	CD4 molecule
RHOV	73.68	18.46	2.00	.00	0.00	ras homolog family member V
HSPA6	9.28	45.70	2.30	.00	0.00	heat shock 70kDa protein 6 (HSP70B′)
MS4A6A	10.71	48.33	2.17	.00	0.00	membrane-spanning 4-domains, subfamily A, member 6A
IL2RG	12.03	50.63	2.07	.00	0.00	interleukin 2 receptor, gamma
CPVL	15.68	57.18	1.87	.00	0.00	carboxypeptidase, vitellogenic-like
CCDC80	32.09	83.18	1.37	.00	0.00	coiled-coil domain containing 80
ZYX	52.97	112.92	1.09	.00	0.00	zyxin
IL7R	5.71	37.49	2.72	.00	0.00	interleukin 7 receptor
NKG7	9.47	45.09	2.25	.00	0.00	natural killer cell group 7 sequence
DHCR24	121.21	44.92	1.43	.00	0.00	24-dehydrocholesterol reductase
CTSH	46.92	103.81	1.15	.00	0.00	cathepsin H
LAP3	38.17	91.33	1.26	.00	0.00	leucine aminopeptidase 3
FHL1	16.36	57.24	1.81	.00	0.00	four and a half LIM domains 1
TSC22D3	57.91	118.68	1.04	.00	0.00	TSC22 domain family, member 3
FPR3	5.53	36.42	2.72	.00	0.00	formyl peptide receptor 3
LILRB5	2.06	28.09	3.77	.00	0.00	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 5
WFDC5	9.64	44.82	2.22	.00	0.00	WAP four-disulfide core domain 5
SOCS3	19.16	61.57	1.68	.00	0.00	suppressor of cytokine signaling 3
EGR1	37.49	89.54	1.26	.00	0.00	early growth response 1
ICAM1	10.60	46.11	2.12	.00	0.00	intercellular adhesion molecule 1
MRC1	3.37	30.89	3.19	.00	0.00	mannose receptor, C type 1
FERMT3	11.32	47.32	2.06	.00	0.00	fermitin family member 3
HMHA1	11.98	48.42	2.02	.00	0.00	histocompatibility (minor) HA-1
IL36RN	22.86	66.76	1.55	.00	0.00	interleukin 36 receptor antagonist
PBXIP1	26.35	72.05	1.45	.00	0.00	pre-B-cell leukemia homeobox interacting protein 1
CST7	9.48	43.52	2.20	.00	0.00	cystatin F (leukocystatin)
TNFRSF1B	16.19	55.50	1.78	.00	0.00	tumor necrosis factor receptor superfamily, member 1B
CD2	8.12	40.68	2.33	.00	0.00	CD2 molecule
GLIPR2	10.81	45.76	2.08	.00	0.00	GLI pathogenesis-related 2

(*continued on next page*)

Table S2. Continued

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
ARHGAP30	9.09	42.46	2.22	.00	0.00	Rho GTPase activating protein 30
CD177	55.29	11.73	2.24	.00	0.00	CD177 molecule
PDLIM3	2.17	26.94	3.64	.00	0.00	PDZ and LIM domain 3
HTRA3	17.26	56.72	1.72	.00	0.00	HtrA serine peptidase 3
MT1E	109.18	40.20	1.44	.00	0.00	metallothionein 1E
LOC645638	37.93	87.87	1.21	.00	0.00	WDNM1-like pseudogene
CAPNS2	86.28	27.63	1.64	.00	0.00	calpain, small subunit 2
ICAM3	23.02	65.34	1.51	.00	0.00	intercellular adhesion molecule 3
ZAP70	5.54	34.28	2.63	.00	0.00	zeta-chain (TCR) associated protein kinase 70kDa
CYBB	7.34	37.78	2.36	.00	0.00	cytochrome b-245, beta polypeptide
PLEKHO1	22.30	63.66	1.51	.00	0.00	pleckstrin homology domain containing, family O member 1
DEFB4B	0.00	22.02	5.46	.00	0.00	defensin, beta 4B
LCP2	5.71	33.87	2.57	.00	0.00	lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)
CD97	8.34	39.17	2.23	.00	0.00	CD97 molecule
TMEM176A	40.75	90.21	1.15	.00	0.00	transmembrane protein 176A
CD27	17.83	55.81	1.65	.00	0.00	CD27 molecule
ISLR	34.05	80.30	1.24	.00	0.00	immunoglobulin superfamily containing leucine-rich repeat
CRLF1	6.29	34.66	2.46	.00	0.00	cytokine receptor-like factor 1
DNAJA4	26.30	68.69	1.39	.00	0.00	DnaJ (Hsp40) homolog, subfamily A, member 4
CIITA	5.50	32.89	2.58	.00	0.00	class II, major histocompatibility complex, transactivator
RUNX3	6.88	35.66	2.37	.00	0.00	runt-related transcription factor 3
TAGAP	3.10	27.32	3.14	.00	0.00	T-cell activation RhoGTPase activating protein
LOC100133286	128.93	54.14	1.25	.00	0.00	uncharacterized LOC100133286
PTPRC	5.10	31.56	2.63	.00	0.00	protein tyrosine phosphatase, receptor type, C
LCK	5.73	32.74	2.52	.00	0.00	lymphocyte-specific protein tyrosine kinase
COX7B	180.87	88.11	1.04	.00	0.00	cytochrome c oxidase subunit VIIb
SPOCK2	3.51	27.52	2.97	.00	0.00	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 2
UBE2L6	37.88	83.86	1.15	.00	0.00	ubiquitin-conjugating enzyme E2L 6
PSMB10	45.45	94.27	1.05	.00	0.00	proteasome (prosome, macropain) subunit, beta type, 10
ADIPOQ	0.00	22.76	7.91	.00	0.00	adiponectin, C1Q and collagen domain containing
EVL	27.62	68.85	1.32	.00	0.00	Enah/Vasp-like
TPM2	38.89	84.85	1.13	.00	0.00	tropomyosin 2 (beta)
ALOX12	42.67	7.95	2.42	.00	0.00	arachidonate 12-lipoxygenase
PLEKHO2	13.51	46.50	1.78	.00	0.00	pleckstrin homology domain containing, family O member 2
SCARA5	16.57	51.53	1.64	.00	0.00	scavenger receptor class A, member 5 (putative)
GSTT1	0.00	19.80	5.31	.00	0.00	glutathione S-transferase theta 1
FMNL1	10.13	40.41	2.00	.00	0.00	formin-like 1
GBP2	21.77	59.47	1.45	.00	0.00	guanylate binding protein 2, interferon-inducible
RRAD	14.11	47.16	1.74	.00	0.00	Ras-related associated with diabetes
ARL4D	62.01	17.33	1.84	.00	0.00	ADP-ribosylation factor-like 4D
RND3	27.35	67.74	1.31	.00	0.00	Rho family GTPase 3
CTSG	29.44	70.71	1.26	.00	0.00	cathepsin G
CD3D	9.51	38.84	2.03	.00	0.00	CD3d molecule, delta (CD3-TCR complex)
TRIM22	22.49	60.31	1.42	.00	0.00	tripartite motif containing 22
VSIG4	5.61	31.12	2.47	.00	0.00	V-set and immunoglobulin domain containing 4
FGFR3	71.55	22.64	1.66	.00	0.00	fibroblast growth factor receptor 3
MAL2	90.74	33.45	1.44	.00	0.00	mal, T-cell differentiation protein 2 (gene/pseudogene)
RBP4	0.00	18.97	5.70	.00	0.00	retinol binding protein 4, plasma
PLEK	6.07	31.78	2.39	.00	0.00	pleckstrin
GPD1	0.00	19.44	6.69	.00	0.00	glycerol-3-phosphate dehydrogenase 1 (soluble)
THBS2	29.35	69.78	1.25	.00	0.00	thrombospondin 2
ARHGAP4	13.65	45.50	1.74	.00	0.00	Rho GTPase activating protein 4
HCST	13.21	44.49	1.75	.00	0.00	hematopoietic cell signal transducer
COL17A1	145.71	68.14	1.10	.00	0.00	collagen, type XVII, alpha 1
ARID5A	15.47	48.08	1.64	.00	0.00	AT rich interactive domain 5A (MRF1-like)
CXCL1	42.36	8.66	2.29	.00	0.00	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)
XIST	0.00	24.52	9.34	.00	0.00	X inactive specific transcript (non-protein coding)
IL2RB	2.93	24.15	3.04	.00	0.00	interleukin 2 receptor, beta

(*continued on next page*)

Table S2. Continued

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
GZMM	5.36	29.36	2.45	.00	0.00	granzyme M (lymphocyte met-ase 1)
SLN	0.00	18.61	4.54	.00	0.00	sarcolipin
KLHL41	0.00	17.77	5.91	.00	0.00	kelch-like family member 41
MARCO	0.00	18.81	4.26	.00	0.00	macrophage receptor with collagenous structure
ARHGEF1	26.59	63.76	1.26	.00	0.00	Rho guanine nucleotide exchange factor (GEF) 1
TMC8	5.81	29.66	2.35	.00	0.00	transmembrane channel-like 8
CXCL17	42.80	9.46	2.18	.00	0.00	chemokine (C-X-C motif) ligand 17
RARRES3	18.23	50.77	1.48	.00	0.00	retinoic acid receptor responder (tazarotene induced) 3
DUSP2	3.85	25.19	2.71	.00	0.00	dual specificity phosphatase 2
CCR7	2.69	22.53	3.07	.00	0.00	chemokine (C-C motif) receptor 7
MEDAG	2.68	22.47	3.07	.00	0.00	mesenteric estrogen-dependent adipogenesis
IL36G	16.30	47.55	1.54	.00	0.00	interleukin 36, gamma
DSC2	132.94	62.08	1.10	.00	0.00	desmocollin 2
LPAR6	46.41	11.39	2.03	.00	0.00	lysophosphatidic acid receptor 6
RNASE7	7.81	32.87	2.07	.00	0.00	ribonuclease, RNase A family, 7
ARRB2	15.75	46.42	1.56	.00	0.00	arrestin, beta 2
DPYSL3	15.69	46.31	1.56	.00	0.00	dihydropyrimidinase-like 3
GAS5	153.94	76.19	1.01	.00	0.00	growth arrest-specific 5 (non-protein coding)
FCGR3A	5.09	27.48	2.43	.00	0.00	Fc fragment of IgG, low affinity IIIa, receptor (CD16a)
LITAF	29.44	66.48	1.18	.00	0.00	lipopolysaccharide-induced TNF factor
TIMP3	32.57	70.70	1.12	.00	0.00	TIMP metallopeptidase inhibitor 3
AKNA	6.52	30.07	2.20	.00	0.00	AT-hook transcription factor
ACAP1	7.20	31.34	2.12	.00	0.00	ArfGAP with coiled-coil, ankyrin repeat and PH domains 1
CA3	0.00	16.61	4.84	.00	0.00	carbonic anhydrase III, muscle specific
LGALS9	10.46	37.02	1.82	.00	0.00	lectin, galactoside-binding, soluble, 9
ADCY7	9.78	35.81	1.87	.00	0.00	adenylate cyclase 7
IL20RB	72.98	26.02	1.49	.00	0.00	interleukin 20 receptor beta
PITX2	28.41	3.96	2.84	.00	0.00	paired-like homeodomain 2
HEPHL1	8.01	32.47	2.02	.00	0.00	hephaestin-like 1
ANGPTL2	23.62	57.41	1.28	.00	0.00	angiopoietin-like 2
ADAMTS1	6.15	28.88	2.23	.00	0.00	ADAM metallopeptidase with thrombospondin type 1 motif, 1
HSPA7	7.36	31.15	2.08	.00	0.00	heat shock 70kDa protein 7 (HSP70B)
CD83	3.22	22.65	2.81	.00	0.00	CD83 molecule
SLAMF8	4.41	25.14	2.51	.00	0.00	SLAM family member 8
RASSF4	11.14	37.62	1.76	.00	0.00	Ras association (RalGDS/AF-6) domain family member 4
COX7A2	148.29	73.96	1.00	.00	0.00	cytochrome c oxidase subunit VIIa polypeptide 2 (liver)
PRG4	0.00	16.19	4.64	.00	0.00	p53-responsive gene 4
NCKAP1L	5.28	26.80	2.34	.00	0.00	NCK-associated protein 1-like
NAPSB	8.63	33.10	1.94	.00	0.00	napsin B aspartic peptidase, pseudogene
C1orf63	28.16	63.30	1.17	.00	0.00	chromosome 1 open reading frame 63
LRP1	30.61	66.71	1.12	.00	0.00	low density lipoprotein receptor-related protein 1
ADH7	38.52	8.47	2.19	.00	0.00	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide
CD8A	4.01	24.12	2.59	.00	0.00	CD8a molecule
SELL	3.73	23.39	2.65	.00	0.00	selectin L
AMICA1	6.66	29.21	2.13	.00	0.00	adhesion molecule, interacts with CXADR antigen 1
TNS1	14.26	42.23	1.57	.00	0.00	tensin 1
TPP1	23.29	55.89	1.26	.00	0.00	tripeptidyl peptidase I
C16orf54	1.85	18.77	3.35	.00	0.00	chromosome 16 open reading frame 54
WIPF1	11.81	38.05	1.69	.00	0.00	WAS/WASL interacting protein family, member 1
LOC284454	14.12	41.79	1.57	.00	0.00	uncharacterized LOC284454
CYTH4	7.93	31.29	1.98	.00	0.00	cytohesin 4
MYL1	0.00	15.29	4.90	.00	0.00	myosin, light chain 1, alkali; skeletal, fast
TNNI2	1.99	18.96	3.25	.00	0.00	troponin I type 2 (skeletal, fast)
FCGR2A	4.73	25.03	2.40	.00	0.00	Fc fragment of IgG, low affinity IIa, receptor (CD32)
CD48	9.61	34.12	1.83	.00	0.00	CD48 molecule
CXCL11	0.00	15.02	5.36	.00	0.00	chemokine (C-X-C motif) ligand 11
SASH3	9.62	34.08	1.83	.00	0.00	SAM and SH3 domain containing 3
CFH	31.43	66.61	1.08	.00	0.00	complement factor H
IRF9	32.47	67.94	1.06	.00	0.00	interferon regulatory factor 9
EBPL	52.47	16.02	1.71	.00	0.00	emopamil binding protein-like
CTSL1	35.43	71.82	1.02	.00	0.00	cathepsin L1

(*continued on next page*)

Table S2. Continued

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
CIDEC	0.00	16.50	7.88	.00	0.00	cell death-inducing DFFA-like effector c
GPR183	4.90	24.94	2.35	.00	0.00	G protein-coupled receptor 183
CD163L1	3.04	20.99	2.79	.00	0.00	CD163 molecule-like 1
PLA2G16	6.94	28.85	2.05	.00	0.00	phospholipase A2, group XVI
TBC1D10C	9.84	33.96	1.79	.00	0.00	TBC1 domain family, member 10C
CLCA2	109.71	50.40	1.12	.00	0.00	chloride channel accessory 2
CSF2RB	12.21	37.89	1.63	.00	0.00	colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)
PIM2	8.53	31.59	1.89	.00	0.00	pim-2 oncogene
HCK	7.81	30.31	1.96	.00	0.00	hemopoietic cell kinase
ATP2A3	15.76	43.38	1.46	.00	0.00	ATPase, Ca++ transporting, ubiquitous
MYO1F	7.11	28.69	2.01	.00	0.00	myosin IF
GBP5	1.90	17.76	3.22	.00	0.00	guanylate binding protein 5
SLC15A3	12.11	37.01	1.61	.00	0.00	solute carrier family 15, member 3
THEMIS2	8.83	31.42	1.83	.00	0.00	thymocyte selection associated family member 2
UQCRQ	95.76	42.43	1.17	.00	0.00	ubiquinol-cytochrome c reductase, complex III subunit VII, 9.5kDa
DEDD2	22.26	52.20	1.23	.00	0.00	death effector domain containing 2
CSRP3	0.00	14.69	7.19	.00	0.00	cysteine and glycine-rich protein 3 (cardiac LIM protein)
EEF1A2	1.42	16.34	3.53	.00	0.00	eukaryotic translation elongation factor 1 alpha 2
COLEC12	6.57	27.21	2.05	.00	0.00	collectin sub-family member 12
PTPN6	17.39	44.85	1.37	.00	0.00	protein tyrosine phosphatase, non-receptor type 6
LGALS2	10.29	33.65	1.71	.00	0.00	lectin, galactoside-binding, soluble, 2
GSTA4	56.46	19.10	1.56	.00	0.00	glutathione S-transferase alpha 4
PCOLCE2	0.00	13.87	4.86	.00	0.00	procollagen C-endopeptidase enhancer 2
PSTPIP1	3.40	20.82	2.62	.00	0.00	proline-serine-threonine phosphatase interacting protein 1
ETS1	15.09	41.27	1.45	.00	0.00	v-ets erythroblastosis virus E26 oncogene homolog 1 (avian)
F10	4.61	23.20	2.33	.00	0.00	coagulation factor X
FXYD6	5.27	24.47	2.22	.00	0.00	FXYD domain containing ion transport regulator 6
SPTBN1	27.16	58.27	1.10	.00	0.00	spectrin, beta, non-erythrocytic 1
ADAM8	5.78	25.17	2.12	.00	0.00	ADAM metallopeptidase domain 8
LENG8	22.68	51.90	1.19	.00	0.00	leukocyte receptor cluster (LRC) member 8
SDC3	14.51	39.83	1.46	.00	0.00	syndecan 3
BIN1	9.32	31.46	1.76	.00	0.00	bridging integrator 1
TTYH3	18.75	46.16	1.30	.00	0.00	tweety homolog 3 (Drosophila)
IGFLR1	9.37	31.42	1.75	.00	0.00	IGF-like family receptor 1
WAS	7.73	28.55	1.89	.00	0.00	Wiskott-Aldrich syndrome
EHF	57.53	20.28	1.50	.00	0.00	ets homologous factor
GDF10	2.80	18.89	2.75	.00	0.00	growth differentiation factor 10
SECTM1	17.76	44.41	1.32	.00	0.00	secreted and transmembrane 1
TNFRSF14	29.06	60.23	1.05	.00	0.00	tumor necrosis factor receptor superfamily, member 14
CP	3.25	19.77	2.60	.00	0.00	ceruloplasmin (ferroxidase)
EFEMP1	20.30	47.97	1.24	.00	0.00	EGF containing fibulin-like extracellular matrix protein 1
KLK9	7.52	27.77	1.88	.00	0.00	kallikrein-related peptidase 9
MYO1G	5.19	23.48	2.18	.00	0.00	myosin IG
PTHLH	2.92	18.83	2.69	.00	0.00	parathyroid hormone-like hormone
DAB2	11.30	34.00	1.59	.00	0.00	Dab, mitogen-responsive phosphoprotein, homolog 2 (Drosophila)
CHRDL1	9.86	31.64	1.68	.00	0.00	chordin-like 1
COA3	106.80	51.38	1.06	.00	0.00	cytochrome c oxidase assembly factor 3
KLRK1	2.90	18.68	2.69	.00	0.00	killer cell lectin-like receptor subfamily K, member 1
BATF	11.08	33.58	1.60	.00	0.00	basic leucine zipper transcription factor, ATF-like
CCR4	1.21	14.69	3.60	.00	0.00	chemokine (C-C motif) receptor 4
CYTIP	4.12	21.16	2.36	.00	0.00	cytohesin 1 interacting protein
ALOX12B	5.94	24.64	2.05	.00	0.00	arachidonate 12-lipoxygenase, 12R type
IGSF6	3.89	20.64	2.41	.00	0.00	immunoglobulin superfamily, member 6
SIGLEC1	1.63	15.61	3.26	.00	0.01	sialic acid binding Ig-like lectin 1, sialoadhesin
IMPA2	77.20	32.65	1.24	.00	0.01	inositol(myo)-1(or 4)-monophosphatase 2
NFE2L2	83.23	36.45	1.19	.00	0.01	nuclear factor (erythroid-derived 2)-like 2
SEMA4B	69.37	27.93	1.31	.00	0.01	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4B
C3AR1	4.32	21.39	2.31	.00	0.01	complement component 3a receptor 1
MAN1A1	15.34	39.85	1.38	.00	0.01	mannosidase, alpha, class 1A, member 1

(*continued on next page*)

Table S2. Continued

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
NCF2	5.09	22.85	2.17	.00	0.01	neutrophil cytosolic factor 2
MMP9	11.07	33.17	1.58	.00	0.01	matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)
GZMK	6.80	25.94	1.93	.00	0.01	granzyme K (granzyme 3; tryptase II)
FAM162A	112.92	56.05	1.01	.00	0.01	family with sequence similarity 162, member A
ASPN	29.74	6.48	2.20	.00	0.01	asporin
PREX1	8.08	28.12	1.80	.00	0.01	phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 1
MARCKSL1	24.92	53.38	1.10	.00	0.01	MARCKS-like 1
GADD45B	19.12	45.17	1.24	.00	0.01	growth arrest and DNA-damage-inducible, beta
CXCR7	10.20	31.58	1.63	.00	0.01	chemokine (C-X-C motif) receptor 7
MFAP5	0.00	12.87	4.26	.00	0.01	microfibrillar associated protein 5
MX1	27.53	56.85	1.05	.00	0.01	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)
CTSW	2.83	18.04	2.67	.00	0.01	cathepsin W
TNFSF12-TNFSF13	13.45	36.66	1.45	.00	0.01	TNFSF12-TNFSF13 readthrough
KLF5	55.23	19.95	1.47	.00	0.01	Kruppel-like factor 5 (intestinal)
DPYSL2	18.82	44.55	1.24	.00	0.01	dihydropyrimidinase-like 2
1-seq	12.19	34.61	1.51	.00	0.01	septin 1
CFP	3.50	19.31	2.47	.00	0.01	complement factor properdin
RCSD1	5.19	22.61	2.12	.00	0.01	RCSD domain containing 1
MIR3610	14.63	38.22	1.39	.00	0.01	microRNA 3610
RASSF2	7.81	27.31	1.81	.00	0.01	Ras association (RalGDS/AF-6) domain family member 2
C11orf96	12.73	35.28	1.47	.00	0.01	chromosome 11 open reading frame 96
AOX1	3.89	20.02	2.36	.00	0.01	aldehyde oxidase 1
ITGAL	3.45	19.09	2.47	.00	0.01	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)
TLN1	23.28	50.45	1.12	.00	0.01	talin 1
EIF1AY	13.66	0.00	4.77	.00	0.01	eukaryotic translation initiation factor 1A, Y-linked
NTN1	5.26	22.57	2.10	.00	0.01	netrin 1
CHI3L2	3.88	19.84	2.35	.00	0.01	chitinase 3-like 2
CECR1	9.82	30.42	1.63	.00	0.01	cat eye syndrome chromosome region, candidate 1
DUSP6	14.45	37.65	1.38	.00	0.01	dual specificity phosphatase 6
LILRB4	3.08	18.14	2.56	.00	0.01	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 4
HAPLN3	18.73	43.90	1.23	.00	0.01	hyaluronan and proteoglycan link protein 3
GIMAP7	22.36	48.98	1.13	.00	0.01	GTPase, IMAP family member 7
MOB3A	15.08	38.51	1.35	.00	0.01	MOB kinase activator 3A
CD247	4.08	20.03	2.30	.00	0.01	CD247 molecule
MS4A4A	5.17	22.11	2.10	.00	0.01	membrane-spanning 4-domains, subfamily A, member 4A
CD6	4.10	20.04	2.29	.00	0.01	CD6 molecule
PAMR1	1.73	14.89	3.11	.00	0.01	peptidase domain containing associated with muscle regeneration 1
CSF1	10.01	30.37	1.60	.00	0.01	colony stimulating factor 1 (macrophage)
PKN1	19.26	44.30	1.20	.00	0.01	protein kinase N1
IDO1	1.72	14.81	3.11	.00	0.01	indoleamine 2,3-dioxygenase 1
COX6A2	0.00	11.68	4.55	.00	0.01	cytochrome c oxidase subunit VIa polypeptide 2
GYPC	16.34	39.92	1.29	.00	0.01	glycophorin C (Gerbich blood group)
RFTN1	13.53	35.63	1.40	.00	0.01	raftlin, lipid raft linker 1
FCGR2B	4.40	20.33	2.21	.00	0.01	Fc fragment of IgG, low affinity IIb, receptor (CD32)
ADIPOQ-AS1	0.00	16.89	10.21	.00	0.01	ADIPOQ antisense RNA 1
MAFF	8.90	28.12	1.66	.00	0.01	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)
PI16	5.86	22.87	1.97	.00	0.01	peptidase inhibitor 16
PIK3IP1	16.08	39.09	1.28	.00	0.01	phosphoinositide-3-kinase interacting protein 1
SLIT3	12.52	33.77	1.43	.00	0.01	slit homolog 3 (Drosophila)
TIGIT	1.42	13.71	3.27	.00	0.01	T cell immunoreceptor with Ig and ITIM domains
KLRC4-KLRK1	2.36	15.85	2.75	.00	0.01	KLRC4-KLRK1 readthrough
TRIB1	6.10	23.15	1.92	.00	0.01	tribbles homolog 1 (Drosophila)
DOCK2	2.79	16.69	2.58	.00	0.01	dedicator of cytokinesis 2
PRF1	3.56	18.23	2.35	.00	0.01	perforin 1 (pore forming protein)
NCF4	9.19	28.22	1.62	.00	0.01	neutrophil cytosolic factor 4, 40kDa

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Table S2. Continued

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
BIRC3	2.86	16.75	2.55	.00	0.01	baculoviral IAP repeat containing 3
EMILIN2	4.68	20.39	2.12	.00	0.01	elastin microfibril interfacer 2
C1orf162	5.45	21.76	2.00	.00	0.01	chromosome 1 open reading frame 162
CD5	2.37	15.64	2.72	.00	0.01	CD5 molecule
C4orf26	12.16	0.00	5.04	.00	0.01	chromosome 4 open reading frame 26
PARVG	3.67	18.33	2.32	.00	0.01	parvin, gamma
IL16	5.52	21.73	1.98	.00	0.01	interleukin 16
USMG5	82.69	38.64	1.10	.00	0.01	up-regulated during skeletal muscle growth 5 homolog (mouse)
VOPP1	25.60	51.63	1.01	.00	0.01	vesicular, overexpressed in cancer, prosurvival protein 1
ENDOU	34.13	9.76	1.81	.00	0.01	endonuclease, polyU-specific
SH2B3	6.73	23.77	1.82	.00	0.01	SH2B adaptor protein 3
GIMAP5	21.29	45.67	1.10	.00	0.01	GTPase, IMAP family member 5
LAIR1	4.70	20.06	2.09	.00	0.02	leukocyte-associated immunoglobulin-like receptor 1
TNFSF12	25.79	51.60	1.00	.00	0.02	tumor necrosis factor (ligand) superfamily, member 12
OAT	69.63	30.64	1.18	.00	0.02	ornithine aminotransferase
GIMAP1-GIMAP5	21.82	46.07	1.08	.00	0.02	GIMAP1-GIMAP5 readthrough
MT1G	19.54	3.12	2.65	.00	0.02	metallothionein 1G
SIK1	13.27	33.81	1.35	.00	0.02	salt-inducible kinase 1
FGD2	6.70	23.37	1.80	.00	0.02	FYVE, RhoGEF and PH domain containing 2
CCDC88B	6.58	23.14	1.81	.00	0.02	coiled-coil domain containing 88B
SNCG	16.79	38.90	1.21	.00	0.02	synuclein, gamma (breast cancer-specific protein 1)
RNF213	5.42	21.08	1.96	.00	0.02	ring finger protein 213
LAT2	7.09	23.97	1.76	.00	0.02	linker for activation of T cells family, member 2
MIR4523	4.20	18.78	2.16	.00	0.02	microRNA 4523
TNFRSF4	4.31	18.98	2.14	.00	0.02	tumor necrosis factor receptor superfamily, member 4
GPR87	34.87	10.44	1.74	.00	0.02	G protein-coupled receptor 87
MS4A7	5.05	20.33	2.01	.00	0.02	membrane-spanning 4-domains, subfamily A, member 7
DSC3	63.59	27.15	1.23	.00	0.02	desmocollin 3
ARHGAP9	5.81	21.70	1.90	.00	0.02	Rho GTPase activating protein 9
LAT	7.78	25.03	1.69	.00	0.02	linker for activation of T cells
SLC9A3	15.54	1.71	3.19	.00	0.02	solute carrier family 9, subfamily A (NHE3, cation proton antiporter 3), member 3
NQO1	34.64	10.42	1.73	.00	0.02	NAD(P)H dehydrogenase, quinone 1
ADAMTSL4	7.06	23.75	1.75	.00	0.02	ADAMTS-like 4
SPINK6	0.00	9.99	6.22	.00	0.02	serine peptidase inhibitor, Kazal type 6
SYTL1	77.09	35.86	1.10	.00	0.02	synaptotagmin-like 1
FYB	2.43	15.03	2.63	.00	0.02	FYN binding protein
MPZL2	85.61	41.52	1.04	.00	0.02	myelin protein zero-like 2
ADRA2A	12.32	31.99	1.38	.00	0.02	adrenoceptor alpha 2A
CD209	3.01	16.19	2.43	.00	0.02	CD209 molecule
CXCR3	4.19	18.51	2.14	.00	0.02	chemokine (C-X-C motif) receptor 3
RNF166	10.17	28.63	1.49	.00	0.02	ring finger protein 166
CTSC	12.70	32.46	1.35	.00	0.02	cathepsin C
FOXP3	1.09	11.78	3.44	.00	0.02	forkhead box P3
OAS3	7.04	23.48	1.74	.00	0.02	2′-5′-oligoadenylate synthetase 3, 100kDa
ELN	15.56	36.55	1.23	.00	0.02	elastin
FAM3B	17.80	2.65	2.75	.00	0.02	family with sequence similarity 3, member B
CLDN17	18.68	40.93	1.13	.00	0.02	claudin 17
TRAF1	3.72	17.45	2.23	.00	0.02	TNF receptor-associated factor 1
TMEM134	77.67	36.68	1.08	.00	0.02	transmembrane protein 134
CLDN7	46.29	17.20	1.43	.00	0.02	claudin 7
RAPGEFL1	32.58	9.63	1.76	.00	0.02	Rap guanine nucleotide exchange factor (GEF)-like 1
TNFSF13	7.41	23.88	1.69	.00	0.02	tumor necrosis factor (ligand) superfamily, member 13
INPP5D	6.50	22.32	1.78	.00	0.02	inositol polyphosphate-5-phosphatase, 145kDa
CBX6	10.94	29.46	1.43	.00	0.02	chromobox homolog 6
STK10	6.30	21.96	1.80	.00	0.02	serine/threonine kinase 10
RASAL3	6.46	22.21	1.78	.00	0.02	RAS protein activator like 3
KCTD12	22.20	45.38	1.03	.00	0.02	potassium channel tetramerisation domain containing 12
ITGAM	2.33	14.37	2.63	.00	0.02	integrin, alpha M (complement component 3 receptor 3 subunit)
OSR1	6.33	21.91	1.79	.00	0.02	odd-skipped related 1 (Drosophila)
TIMM8B	80.79	38.99	1.05	.00	0.02	translocase of inner mitochondrial membrane 8 homolog B (yeast)

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Table S2. Continued

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
CTLA4	0.00	10.61	3.83	.00	0.02	cytotoxic T-lymphocyte-associated protein 4
MYLPF	0.00	9.39	5.40	.00	0.02	myosin light chain, phosphorylatable, fast skeletal muscle
SPN	1.67	12.85	2.94	.00	0.03	sialophorin
KCNAB2	4.72	19.01	2.01	.00	0.03	potassium voltage-gated channel, shaker-related subfamily, beta member 2
SLA	5.03	19.56	1.96	.00	0.03	Src-like-adaptor
SRPX	11.35	29.86	1.40	.00	0.03	sushi-repeat containing protein, X-linked
MTRNR2L10	84.76	41.81	1.02	.00	0.03	MT-RNR2-like 10
PGAM2	5.15	19.71	1.94	.00	0.03	phosphoglycerate mutase 2 (muscle)
SERPINE1	4.44	18.37	2.05	.00	0.03	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1
RGS10	21.46	44.06	1.04	.00	0.03	regulator of G-protein signaling 10
TGOLN2	20.64	42.91	1.06	.00	0.03	trans-golgi network protein 2
FAM107B	7.08	22.93	1.70	.00	0.03	family with sequence similarity 107, member B
MYBPC1	0.00	10.73	8.20	.00	0.03	myosin binding protein C, slow type
MIR27A	1.88	13.15	2.81	.00	0.03	microRNA 27a
NLRC5	6.59	22.01	1.74	.00	0.03	NLR family, CARD domain containing 5
CCR1	1.86	13.03	2.81	.00	0.03	chemokine (C-C motif) receptor 1
APOBR	2.54	14.47	2.51	.00	0.03	apolipoprotein B receptor
ITK	1.32	11.72	3.15	.00	0.03	IL2-inducible T-cell kinase
PTGER4	5.05	19.25	1.93	.00	0.03	prostaglandin E receptor 4 (subtype EP4)
CCDC69	19.15	40.50	1.08	.00	0.03	coiled-coil domain containing 69
RHOF	8.24	24.53	1.57	.00	0.03	ras homolog family member F (in filopodia)
TNNT3	2.24	13.70	2.62	.00	0.03	troponin T type 3 (skeletal, fast)
GZMB	4.13	17.43	2.08	.00	0.03	granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1)
PILRA	2.82	14.88	2.40	.00	0.03	paired immunoglobin-like type 2 receptor alpha
APOBEC3G	5.41	19.72	1.87	.00	0.03	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G
CLIC2	4.64	18.33	1.98	.00	0.03	chloride intracellular channel 2
MYH2	0.00	8.96	6.23	.00	0.03	myosin, heavy chain 2, skeletal muscle, adult
PLCB2	3.43	16.03	2.22	.00	0.03	phospholipase C, beta 2
STAT5A	8.92	25.45	1.51	.00	0.03	signal transducer and activator of transcription 5A
MYO9B	11.26	29.02	1.37	.00	0.03	myosin IXB
PTPN7	2.30	13.72	2.57	.00	0.03	protein tyrosine phosphatase, non-receptor type 7
FAIM3	3.02	15.18	2.33	.00	0.03	Fas apoptotic inhibitory molecule 3
LIMD2	10.74	28.22	1.39	.00	0.03	LIM domain containing 2
MMP13	10.68	0.00	4.42	.00	0.03	matrix metallopeptidase 13 (collagenase 3)
ITGB7	5.87	20.40	1.80	.00	0.03	integrin, beta 7
IKZF1	2.73	14.54	2.41	.00	0.03	IKAROS family zinc finger 1 (Ikaros)
6-seq	4.09	17.16	2.07	.00	0.04	septin 6
S1PR4	5.29	19.32	1.87	.00	0.04	sphingosine-1-phosphate receptor 4
SLC12A7	9.63	26.39	1.45	.00	0.04	solute carrier family 12 (potassium/chloride transporters), member 7
ZNF750	34.40	11.29	1.61	.00	0.04	zinc finger protein 750
RGCC	21.00	42.39	1.01	.00	0.04	regulator of cell cycle
TNFSF14	0.00	10.50	3.40	.00	0.04	tumor necrosis factor (ligand) superfamily, member 14
GIMAP4	20.62	41.87	1.02	.00	0.04	GTPase, IMAP family member 4
IDS	15.61	34.99	1.16	.00	0.04	iduronate 2-sulfatase
CADM3	10.50	27.48	1.39	.00	0.04	cell adhesion molecule 3
CPXM1	41.56	15.50	1.42	.00	0.04	carboxypeptidase X (M14 family), member 1
MIR638	8.27	24.03	1.54	.00	0.04	microRNA 638
JAK3	5.36	19.22	1.84	.00	0.04	Janus kinase 3
RARA	9.74	26.28	1.43	.00	0.04	retinoic acid receptor, alpha
APOL6	4.62	17.81	1.95	.00	0.04	apolipoprotein L, 6
PIK3CD	5.77	19.79	1.78	.00	0.04	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta
MFNG	11.28	28.48	1.34	.00	0.04	MFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase
GZMA	7.04	21.89	1.64	.00	0.04	granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)
TRPV2	4.14	16.85	2.03	.00	0.04	transient receptor potential cation channel, subfamily V, member 2
CBX7	15.33	34.20	1.16	.00	0.04	chromobox homolog 7

(*continued on next page*)

Table S2. Continued

Gene	*HC*	*OLP*	*|log2(foldchang)|*	P *value*	*Q value*	*Description*
PPP1R16B	3.72	16.03	2.11	.00	0.04	protein phosphatase 1, regulatory subunit 16B
NAA20	68.86	32.76	1.07	.00	0.04	N(alpha)-acetyltransferase 20, NatB catalytic subunit
BIN2	4.05	16.63	2.04	.00	0.04	bridging integrator 2
APOBEC3C	15.35	34.13	1.15	.00	0.04	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3C
ALOX5	8.61	24.23	1.49	.00	0.04	arachidonate 5-lipoxygenase
CSRNP1	7.91	23.11	1.55	.00	0.05	cysteine-serine-rich nuclear protein 1
MYH7	0.00	10.19	8.70	.00	0.05	myosin, heavy chain 7, cardiac muscle, beta
EVI2B	8.17	23.47	1.52	.00	0.05	ecotropic viral integration site 2B
PPP1R1A	0.00	8.47	6.75	.00	0.05	protein phosphatase 1, regulatory (inhibitor) subunit 1A
RENBP	3.52	15.47	2.14	.00	0.05	renin binding protein
S100B	9.44	25.34	1.42	.00	0.05	S100 calcium binding protein B
PGF	11.72	28.73	1.29	.00	0.05	placental growth factor
HSPB2	8.96	24.57	1.46	.00	0.05	heat shock 27kDa protein 2
TNNC2	1.14	10.38	3.19	.00	0.05	troponin C type 2 (fast)
ACSL1	13.40	31.10	1.22	.00	0.05	acyl-CoA synthetase long-chain family member 1