Differentially expressed genes, lncRNAs, and competing endogenous RNAs in Kawasaki disease

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ABSTRACT

Background. Kawasaki disease (KD) is an acute and febrile systemic vasculitis of unknown etiology. This study aimed to identify the competing endogenous RNA (ceRNA) networks of lncRNAs, miRNAs, and genes in KD and explore the molecular mechanisms underlying KD.

Methods. GSE68004 and GSE73464 datasets were downloaded from the Gene Expression Omnibus. Differentially expressed lncRNAs (DElncRNAs) and genes (DEGs) in KD were identified using the criteria of \( p < 0.05 \) and \(| \log_2 \text{(fold change)} | \geq 1\). MicroRNAs (miRNAs) related to KD were searched from databases. The lncRNA-miRNA-mRNA networks involving the DElncRNAs and DEGs were constructed.

Results. A total of 769 common upregulated, 406 common downregulated DEGs, and six DElncRNAs were identified in the KD samples. The lncRNA-miRNA-mRNA network consisted of four miRNAs, three lncRNAs (including the upregulated PSORS1C3, LINC00999, and the downregulated SNHG5) and four DEGs (including the downregulated GATA3 and the upregulated SOD2, MAPK14, and PPARG). Validation in the GSE18606 dataset showed that intravenous immunoglobulin treatment significantly alleviated the deregulated profiles of the above RNAs in KD patients. Three ceRNA networks of LINC00999-hsa-miR-6780-SOD2, PSORS1C3-hsa-miR-216a-PPARG/MAPK14, and SNHG5-hsa-miR-132/hsa-miR-92/GATA3 were identified. Four genes were associated with functional categories, such as inflammatory response and vascular endothelial cell.

Conclusions. The ceRNA networks involve genes, such as SOD2, MAPK14, and PPARG, and lncRNAs, including PSORS1C3, LINC00999, and SNHG5, which might play a key role in the pathogenesis and development of KD by regulating inflammation.

INTRODUCTION

Kawasaki disease (KD), also named mucocutaneous lymph node syndrome, is an acute, self-limiting, and febrile systemic vasculitis. The incidence of KD and rates of hospitalizations for KD are different across nations and ethnicities (Elakabawi et al., 2020; Holman et al., 2010; Kim et al., 2017; Lin & Wu, 2017). The incidence of KD is approximately 200 per 100,000...
children <5 years old worldwide (Kim et al., 2017) and the KD-related hospitalization rate is approximately 20 per 100,000 children (Holman et al., 2010). KD predominantly affects children aged between 6 months and 5 years old. Intravenous immunoglobulin (IVIG) is the major treatment strategy for KD (Kim et al., 2017; Kim & Kim, 2016). The incidence of acute systemic vasculitis and acquired heart disease (including coronary artery abnormality) can be reduced by appropriate and timely treatment with IVIG and aspirin. However, the etiology of KD is largely unknown and the diagnosis of both complete and incomplete KD is challenging.

Many clinical and epidemiologic research studies suggest an infectious etiology for KD (Rowley, 2017; Shulman & Rowley, 2015). Viral respiratory infections are common in KD patients (Maggio, Fabiano & Corsello, 2019; Rosenfeld et al., 2020). KD is an immune-mediated echo of viral infection and viral infection might trigger KD (Rigante, 2020; Rosenfeld et al., 2020). The coronavirus disease (COVID-19) pandemic, characterized by profound hyperinflammation, leads to a missed or delayed diagnosis of KD (Jones et al., 2020; Ouldali et al., 2020; Roe, 2020; Toubiana et al., 2020). Jones et al. (2020) first presented a severe KD infant triggered by COVID-19 (SARS-CoV-2). SARS-CoV-2 infection contributes to a rapid increase in KD incidence (Ouldali et al., 2020). Also, many genetic factors, including genes, microRNAs (miRNA), and long non-coding RNAs (lncRNA), play crucial roles in KD and associate with IVIG resistance and coronary artery lesions (CAL) secondary to KD (Ahn et al., 2019; Kuo et al., 2017; Jones et al., 2020; Ko et al., 2019; Rong et al., 2017; Wang et al., 2019; Wright et al., 2018).

Genes, miRNAs, and lncRNAs play important roles in the regulation of many biological processes. LncRNAs affect gene regulation transcriptionally or post-transcriptionally by sponging miRNAs (Yan et al., 2015; Zhu et al., 2016). For instance, lncRNA myocardial infarction associated transcript (MIAT) regulates cardiac hypertrophy, angiogenesis, and endothelial cell function by sponging miR-150 and miR-150-5p (Yan et al., 2015; Zhu et al., 2016). Also, the competing endogenous RNA (ceRNA) networks of lncRNAs trigger, control, or suppress disease conditions (Leisegang, 2018; Sun et al., 2019). However, there is insufficient information on the regulatory ceRNA networks of lncRNAs in KD. Additional evidence is required to probe into the clues of lncRNAs in KD.

This study was performed to investigate the ceRNA networks of differentially expressed lncRNAs (DElncRNAs) and differentially expressed genes (DEGs) in KD. DElncRNAs and DEGs in the blood samples from patients with KD were identified. The ceRNA mechanisms in KD were identified using integrated bioinformatics analysis of microarray datasets. This study might provide a reference for exploring the pathology of KD.

**MATERIAL AND METHODS**

**Microarray data**
The microarray datasets, GSE68004, GSE73464, and GSE18606, were downloaded from the Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) in August 2020. The GSE68004 dataset (GPL10558, Illumina HumanHT−12 V4.0 expression beadchip) contained 89 blood samples collected from 76 pediatric patients with complete KD, 13...
pediatric patients with incomplete KD, and 37 blood samples from age- and sex-matched healthy controls. The GSE73464 dataset consisted of 839 samples, including 55 samples from healthy controls and 78 samples from patients with KD. The GSE18606 dataset was downloaded and 48 blood samples from nine healthy controls and 20 KD patients (eight IVIG non-responding and 12 IVIG-responding patients) at the acute and convalescent stages. The GSE68004 and GSE73464 datasets were used to screen DElncRNAs and DEGs and the GSE18606 dataset was used to validate the expression profiling.

Data processing
The non-normalized raw data were downloaded and processed using the Limma package (Smyth, 2005). The expression levels of background-corrected and normalized probes were calculated. Probes mapped to human mRNAs and lncRNAs in the GRCh38 human reference genome were retained; otherwise, they were removed. In the case of multiple probes mapped to one mRNA or lncRNA, the mean expression value of the probes was calculated and regarded as the expression level of that mRNA or lncRNA.

Analysis of differential expression
The DEGs and DElncRNAs in the KD samples were screened using the GEO2R analysis tool (http://www.ncbi.nlm.nih.gov/geo/geo2r/). Significant DEGs and DElncRNAs were identified using the criteria of p value <0.05 and |log₂(fold change, FC)|≥1. DEGs and DElncRNAs with log₂FC ≥1 were upregulated, and log₂FC ≤−1 were downregulated, respectively. Common DEGs between the GSE68004 and GSE73464 datasets were retained and used for further analysis.

Identification of KD-related genes databases
The Comparative Toxicogenomics Database (CTD, update 2019; http://ctdbase.org/) is a premier public resource consisting of literature-based and manually curated associations between diseases, genes, pathways, and chemicals (Davis et al., 2019). KD-related genes and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were identified from the CTD database using the search keyword “mucocutaneous lymph node syndrome”. The genes and pathways that overlapped between DEGs and items in the CTD database were retained.

Construction of the protein-protein interaction (PPI) network
The protein interaction pairs were identified in the STRING database (Version 11.0, https://string-db.org/cgi/input.pl) with a score >0.4. The PPI network was constructed using the Cytoscape software (version 3.8.0; https://cytoscape.org/) and network modules were identified using the Molecular Complex Detection (MCODE) plugin of Cytoscape.

Functional enrichment analysis
The annotation of Gene Ontology biological processes and KEGG pathways presents the biological properties of DEGs. Gene Ontology biological processes and KEGG pathways related to DEGs were identified using the database for annotation, visualization, and integrated discovery (DAVID, version 6.7; https://david.ncifcrf.gov/) in this study.
Significant enrichment was identified when the adjusted (BH correction) \( p \) value was <0.05.

**Identification of KD-related miRNAs**

miRNAs related to DEGs in KD were searched in the miRWalk (http://mirwalk.umm.uni-heidelberg.de/), miRTarbase (http://mirtarbase.cuhk.edu.cn/php/index.php), and starBase (version 2.0 https://www.starbaserobins.org/our-programs/starbase-2-0/) databases. The miRNA-mRNA pairs identified from at least two databases were retained and used to construct the miRNA-mRNA regulatory network.

**Construction of the lncRNA-miRNA-mRNA ceRNA network**

The miRNA-lncRNA pairs were obtained from the miRcode (http://www.mircode.org/), DIANA-LncBase v2 (http://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?r=lncbasev2%2Findex-experimental), and starBase (version 2.0; https://www.starbaserobins.org/our-programs/starbase-2-0/) databases. LncRNA-miRNA pairs included in at least two databases were retained and used for the construction of the lncRNA-miRNA network. The ceRNA networks were subsequently constructed using the Cytoscape software.

**Functional clustering of the key items**

GeneCLiP 3.0 (http://ci.smu.edu.cn/genclip3/analysis.php) is a web-based literature mining database providing the functional clustering of potential candidates. The hub DEGs and DElncRNAs in the ceRNA networks were subjected to GeneCLiP3.0. The heatmap of functional clustering was obtained with the criteria of \( p < 0.01 \) and hit \( \geq 4 \).

**RESULTS**

**Identification of DEGs and DElncRNAs in KD**

Based on the criteria of \( p \) value <0.05 and \(|\text{logFC}| \geq 1\), a total of 2721 DEGs (1786 upregulated and 935 downregulated genes) and 1848 DEGs (1161 upregulated and 687 downregulated genes) were identified in the datasets GSE68004 and GSE73464, respectively (Figs. 1A and 1C). We also identified 48 DEI ncRNAs (36 upregulated and 12 downregulated) and 68 DElncRNAs (34 upregulated and 34 downregulated) in the GSE68004 and GSE73464 datasets, respectively (Figs. 1B and 1D). The DEGs and DElncRNAs showed distinctive expression profiles in the KD and control samples in the GSE68004 dataset (Figs. 1E and 1F).

Venn diagram identified 769 common upregulated and 406 common downregulated DEGs between the GSE68004 and GSE73464 datasets (Figs. 1G and 1H). In addition, 5927 KD-related genes were identified in the CTD, including 413 DEGs (308 upregulated and 105 downregulated genes; Fig. 1I; Table S1). Also, six common DElncRNAs were included in the two datasets, including four upregulated (MRVII-AS1, PSORSIC3, MAFA-AS1, and LINC00999) and two downregulated lncRNAs in KD compared with controls (SNHG5 and KLF3-AS1).
Functional analysis of the DEGs

Functional enrichment analysis of the 413 common DEGs showed that the upregulated genes were significantly enriched with 279 biological processes including “GO:0006952 ~ defense response”, “GO:0001817 ~ regulation of cytokine production”, and “GO:0032675 ~ regulation of interleukin-6 production”, and six KEGG pathways, including “hsa04060: Cytokine-cytokine receptor interaction”, “hsa04620: Toll-like receptor signaling pathway”, and “hsa0050870 ~ positive regulation of T cell activation”, and six KEGG pathways, including “hsa05340: Primary immunodeficiency”, “hsa04660: T cell receptor signaling pathway”, and “hsa04060: Cytokine-cytokine receptor interaction” (Table S2). The downregulated genes were associated with 73 biological processes, including “GO:0042110 ~ T cell activation”, “GO:0002694 ~ regulation of leukocyte activation”, and “GO:0050870 ~ positive regulation of T cell activation”, and six KEGG pathways, including “hsa05340: Primary immunodeficiency”, “hsa04660: T cell receptor signaling pathway”, and “hsa04060: Cytokine-cytokine receptor interaction” (Table S2).
The modules and the protein–protein interaction (PPI) network of the differentially expressed genes (DEGs) in Kawasaki disease (KD). (A & B) The PPI network and modules of the upregulated and downregulated DEGs, respectively. Red and green color notes the significant upregulation ($p < 0.05$ and log2Fold change $\geq 1$) and downregulation ($p < 0.05$ and log2Fold change $\leq -1$), respectively.

Construction of the PPI network and functional analysis

The PPI network of the upregulated genes consisted of 101 DEGs and 504 interaction pairs (Fig. 2A). We identified two modules (score $>5$) consisting of 17 and 11 upregulated genes in the upregulated PPI network (Table 1). The PPI network of the downregulated DEGs included 68 DEGs and 213 lines (Fig. 2B). One module consisting of 14 downregulated genes was included in the downregulated PPI network (Fig. 2B). The functional enrichment analysis showed that genes in module 1 of upregulated DEGs were enriched in 44 biological processes, including “GO:0009617 ~ response to bacterium”, “GO:0032496 ~ response to lipopolysaccharide”, “GO:0042981 ~ regulation of apoptosis”, and “GO:0001817 ~ regulation of cytokine production” (Table S3), and one KEGG pathway “hsa04670:Leukocyte transendothelial migration”. None functional categories enriched the DEGs in the other two modules. Genes in three PPI network modules were used to identify miRNA-target pairs.
Table 1  The list of the genes in the modules in the protein–protein network of the upregualted and downregulated genes in Kawasaki disease.

| Module        | Genes                                                                 |
|---------------|----------------------------------------------------------------------|
| Up-Module 1   | MAPK14, THBD, PPARG, ITGAM, FCGR2A, HP, LCN2, SELP1, MPO, SELP, MYD88, IL1R1, MMP9, TIMP1, CASP1, JAK2, SOCS3 |
| Up-Module 2   | DUSP1, SERPINB2, SOD2, IL1B, IL1RN, IL4R, IL1R2, ABCA1, IL10, TLR4, TLR2 |
| Down-Module 1 | GATA3, IL2RB, CD27, CD40LG, CD3D, ZAP70, CD8A, KLRB1, IL7R, CD4, LCK, CD5, RORC, CD86 |

Identification of ceRNAs networks

A total of 423 miRNA-target pairs were identified from databases, including 30 DEGs (nine downregulated and 21 upregulated genes) and 298 miRNAs in the miRNA-mRNA regulatory network (Fig. 3A). Also, we identified 42 lncRNA-miRNA pairs of four DElncRNAs from databases, including two upregulated lncRNAs (PSORSIC3 and LINCO0999) and two downregulated lncRNAs (SNHG5 and KLF3-AS1).

According to the co-expression profiles of the DElncRNAs and DEGs, five lncRNA-miRNA-mRNA pairs were extracted from the lncRNA-miRNA and miRNA-mRNA pairs (Fig. 4A). The upregulated superoxide dismutase 2 (SOD2) gene was regulated by LINCO0999 through hsa-miR-6780. The upregulated genes peroxisome proliferator-activated receptor gamma (PPARG) and mitogen-activated protein kinase 14 (MAPK14) were regulated by lncRNA PSORSIC3 through hsa-miR-216a. Besides, the downregulated lncRNA SNHG5 regulated the GATA binding protein 3 (GATA3) gene through hsa-miR-132 and hsa-miR-92.

Microarray dataset validation of DEGs and DElncRNAs

Figure 4B presents the expression profiling of the seven DEGs and DElncRNAs in KD samples in microarray datasets. LINCO0999, SOD2, PPARG, PSORSIC3, and MAPK14 were upregulated in KD in all datasets, while GATA3 and SNHG5 were downregulated in KD samples in at least two datasets (Fig. 4B). We also observed that the IVIG treatment significantly attenuated the increased levels of LINCO0999, SOD2, PPARG, and MAPK14, and increased the expression levels of SNHG5 and GATA3 in patients with KD (p < 0.05 by t-test, Fig. 4C). These results suggested that the lncRNA-miRNA-mRNA regulatory pairs, including the upregulated LINCO0999-hsa-miR-6780-SOD2 and PSORSIC3-hsa-miR-216a-PPARG/MAPK14 networks and the downregulated SNHG5-hsa-miR-132/hsa-miR-92-GATA3 network, might have crucial roles in the pathology of KD and treatment for KD.

Functional clustering of the hub DElncRNAs and DEGs

The functional clustering of the hub DEGs and DElncRNAs in the lncRNA-miRNA-mRNA ceRNA network is shown in Fig. S1. SNHG5 was associated with four items, including “acute myeloid leukemia”, “ovarian cancer”, “myeloid leukemia”, and “renal cell carcinoma”, and PSORSIC3 was associated with two items, including “DNA methylation” and “psoriasis”.
Four DEGs (SOD2, GATA3, PPARG, and MAPK14) were related to various functional categories, including “inflammatory response”, “cell activation”, “autoimmune disease”, and “vascular endothelial cell” (Fig. S1). These results indicated that DEGs and DElncRNAs were involved in various pathways.

**DISCUSSION**

The association of KD with COVID-19 provides a novel insight into the pathology of KD. Also, the associations of miRNAs and lncRNAs with pandemic COVID-19 suggested the key
roles of them in COVID-19 management (Gambardella et al., 2020; Ramaiah, 2020; Teodori et al., 2020). Our study identified the significantly deregulated genes, lncRNAs, and ceRNA networks in KD. DEGs including SOD2, GATA3, PPARG, and MAPK14 were associated with biological processes related to "inflammatory response". LncRNAs including the downregulated SNHG5 lncRNA and the upregulated LINC00999 and PSORS1C3 lncRNAs might have crucial roles in KD by regulating the above DEGs. Microarray validation showed that the IVIG treatment attenuated the expression of SNHG5, LINC00999, SOD2, GATA3, PPARG, and MAPK14 in patients with KD, indicating the crucial roles of them in KD pathology and treatment.

Among the DElncRNAs in KD patients, SNHG5 regulated GATA3 by sponging hsa-miR-132 and hsa-miR-92. SNHG5 plays an important role in human tumors as an oncogenic lncRNA (Damas et al., 2016; Li et al., 2019b; Li et al., 2018; Zhang et al., 2019). SNHG5 promotes tumor cell proliferation, survival, and drug resistance by sponging miRNAs to enhance gene expression (Damas et al., 2016; Li et al., 2019b; Li et al., 2018; Zhang et al., 2019). Zhang et al. (2019) showed that SNHG5 is upregulated in colorectal cancer tissues and its expression increased cell proliferation, metastasis, and migration by inhibiting miR-132-3p and enhancing CAMP responsive element binding protein 5. Plasma miR-132-5p
might be a diagnostic biomarker for early acute myocardial infarction (Li et al., 2019a). However, the inhibition of miR-132 attenuates cortical inflammation (Mishra et al., 2017). Also, miR-92 exhibits an anti-inflammatory effect and suppresses inflammatory responses in macrophages (Lai et al., 2013). Besides, the GATA3 gene is an essential transcription factor and a critical regulator of immune cell function (Usary et al., 2004; Zhu et al., 2004). GATA3 controls T helper type 2 (Th2) cell differentiation and Foxp3+ regulatory T cell fate (Wohlfert et al., 2011; Zhu et al., 2004). Th2 cells and the GATA3 gene both were involved in airway inflammation (Choi et al., 2016; Jang et al., 2016; Peng et al., 2018). However, this is no direct information showing the association of miR-132/92, SNHG5, and GATA3 with KD. Our study indicated that the expression levels of SNHG5 and GATA3 were downregulated in KD but were enhanced by the IVIG treatment. These results indicated that SNHG5 and GATA3 and the SNHG5-hsa-miR-132/hsa-miR-92-GATA3 axis might have crucial roles in the pathology of KD through regulating inflammation.

Delayed diagnosis and treatment for KD may cause prolonged inflammation of vessel walls and a high risk for IVIG resistance and a high rate of CALs (Lech et al., 2019; Rigante, 2020; Türkuçar et al., 2020). Also, clinical variables, including the levels of platelet-derived microparticles, platelet count, and neutrophil count were associated with CALs (Chen et al., 2011; Hu et al., 2020; Jin et al., 2019). Molecular factors, including the Th2 cytokine thymus, activation-regulated chemokine/chemokine ligand 17 (TARC/CCL17) and the neutrophil hematopoietic cytokine granulocyte colony-stimulating factor (G-CSF) were related to IVIG resistance in KD (Abe et al., 2008; Lee et al., 2013). Patients with KD having an allele of the TARC/CCL17 (rs4784805) had a better response to the IVIG treatment (Lee et al., 2013). Abe et al. (2008) showed that the serum G-CSF levels in IVIG nonresponsive patients were significantly higher than in responsive patients before treatment. These studies indicate the inflammatory biomarkers play critical roles in the pathogenesis of IVIG resistance and CALs in KD.

Oxidative stress contributes to inflammation and tissue injury. Elevated cardiac reactive oxygen species (ROS) accumulation is a common pathologic feature in KD and cardiac hypertrophy (Yahata & Hamaoka, 2017; Zhang et al., 2017). Neutrophil respiratory burst produces ROS and predicts the risk of CALs in KD (Hu et al., 2020). SOD2 is the primary antioxidant enzyme neutralizing $\cdot$O$_2^-$ and its overexpression promotes reductive stress (Zhang et al., 2017). SOD2 prevents cardiac ROS production and hypertrophy features (Xie et al., 2020). These studies showed that SOD2 upregulation might be a self-healing mechanism in KD. However, the associations of hsa-miR-6780, SOD2, and LINC00999 with vasculitis and KD have not been reported till now. Also, microarray validation showed that IVIG treatment attenuated SOD2 and LINC00999 expression levels in the blood samples from patients with KD. These results showed that the ceRNA network of upregulated SOD2 and LINC00999 might protect against oxidative stress-induced damage in KD.

Another upregulated ceRNA network in KD was the PSORS1C3-hsa-miR-216a-PPARG/MAPK14 network. PPAR$\gamma$ is a nuclear hormone receptor predominantly expresses in adipose tissue and involves in adipogenesis (Fang et al., 2016; Son et al., 2007). Son et al. (2007) showed that PPAR$\gamma$1 overexpression increased the expression of fatty acid oxidation genes in mouse hearts. Heart function could be improved by PPAR$\gamma$ agonist (Fang et al.,...
PPARγ is a target of anti-inflammatory drugs including the agonist thiazolidinediones which could ameliorate COVID-19 progression (Carboni, Carta & Carboni, 2020). Besides, MAPK14/p38α regulates inflammatory response (Fazia et al., 2020; Wu et al., 2019). MAPK14 mediates autophagy and activates inflammation and proliferation in vascular smooth muscle cells (VSMCs) through the NF-κB signaling (Wu et al., 2019). Also, miR-216a has an anti-inflammatory effect in in vitro cell models (Kong et al., 2020; Tian et al., 2018; Yang et al., 2018). The upregulation of miR-216a or miR-216a-5p protects cells from oxidative stress-induced injury via targeting the NF-κB and JAK signaling pathways (Kong et al., 2020; Tian et al., 2018; Yan et al., 2019; Yang et al., 2018). Microarray validation showed that the PPARG and MAPK14 genes in KD were decreased following the IVIG treatment in the GSE18606 dataset. These results showed that the PPARG and MAPK14 might be therapeutic targets for KD.

CONCLUSIONS

In conclusion, we confirmed that the ceRNA networks, including the upregulated networks LINC00999-hsa-miR-6780-SOD2 and PSORS1C3-hsa-miR-216a-PPARG/MAPK14 and the downregulated network SNHG5-hsa-miR-132/hsa-miR-92-GATA3, might relate to the pathogenesis of and development of KD. These networks are associated with inflammation and response to IVIG treatment in KD. Our study provides new insights into the pathogenesis of KD. However, the ceRNA networks and their associations with KD should be validated.

ADDITIONAL INFORMATION AND DECLARATIONS

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Competing Interests
The authors declare there are no competing interests.

Author Contributions
- Changsheng Guo conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Yuanqing Hua conceived and designed the experiments, performed the experiments, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Zuanhao Qian conceived and designed the experiments, performed the experiments, authored or reviewed drafts of the paper, and approved the final draft.

Data Availability
The following information was supplied regarding data availability:

The original microarray data is available at the NCBI Gene Expression Omnibus: GSE68004, GSE18606 and GSE73464.
All data generated during this study are contained in the figures and tables (Figs. 1–4; Table 1; Tables S1–S3 and Fig. S1).

**Supplemental Information**

Supplemental information for this article can be found online at [http://dx.doi.org/10.7717/peerj.11169#supplemental-information](http://dx.doi.org/10.7717/peerj.11169#supplemental-information).

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