Scavenger receptor class a, member 3 is associated with severity of hand, foot, and mouth disease in a case-control study

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Abstract

Hand, foot, and mouth disease (HFMD) spreads rapidly and has been recognized as a public health problem in recent years in China. Unfortunately, there is no effective vaccine or antiviral drug currently for EV71 infection. In this study, we aim to identify biomarker which are associated with for severity of EV71 infection cases using high-throughput RNA sequencing approach.

RNA sequencing of samples from severe HFMD (S) patients group (n = 10) and control HFMD (C) patients group (n = 10) were performed and the results were verified by qPCR. mRNA with the highest expression level was selected to be validated in an independent cohort comprising of 45 severe EV71 infected patients and 45 control by qPCR assay.

Seventeen significant differentially expressed genes were identified. Scavenger receptor class A, member 3 (SCARA3) was one of the significantly upregulated genes with the highest expression level and was selected for validation. The mean relative expression levels in severe HFMD and control HFMD patients were 10.1-fold and 5.0-fold, respectively, *P* value <.001.

We found that SCARA3 is associated with severity of HFMD, and it may be a potential prognostic marker to predict the HFMD progression in EV71 infected patients.

Abbreviations: CSF = cerebrospinal fluid, CVA16 = coxsackievirus A16, EV71 = enterovirus 71, HFMD = hand foot mouth disease, SCARA3 = Scavenger receptor class A, member 3, WBC = white blood cell.

Keywords: biomarker, foot and mouth disease, hand, SCARA3

1. Introduction

Hand, foot, and mouth disease (HFMD) is a common infectious diseases in infants and young children and characterized by ulcers on the hand and foot and in the mouth.[1] HFMD can spread and cause outbreaks all over the world which leads to serious public health threat and heavy economic burden.[2–4] In China, the epidemic of HFMD has become a serious public health problem[5–9] and recent outbreaks in Shanghai and Zunyi had over 2,000,000 and 6,000 cases, respectively occurred within 1 year.[10,11]

HFMD is mainly caused by enterovirus 71 (EV71) and coxsackievirus A16 (CVA16).[12,13] Most of HFMD cases caused by CVA16 are mild with symptoms limited to fever, malaise, rashes on the volar regions of the hands and feet, herpangina and difficulty eating and drinking. EV71 associated patients appear to be more severe with high mortality and can cause neurological complications, such as aseptic meningitis, encephalitis, brain stem encephalitis, neurogenic pulmonary edema, and hemorrhage.[1,14,15] Although only 1% of HFMD patients developed cardiopulmonary or neurological complications, the fatality rate was as high as 3% in those severe cases.[16] Therefore, large scale EV71 infection outbreak has huge impact on the society and healthcare system. In recent years, CVA6 has been frequently identified in HFMD outbreaks in many Asian countries including China, Thailand, Japan, and Singapore.[17–21] CVA6 infection is characterized with high fever and abnormal white blood cell (WBC) count in blood.[22,23]

EV71 vaccines had been developed and some of them had completed phase 3 clinical trials.[24] However, there is no single vaccine for all EV71 infections due to the wide genetic diversity of HFMD.[25–27] Therefore it is essential to develop other preventive or interventional methods for better outcome. One of them is to use noninvasive blood markers to identify the severe cases or predict the progression so early intervention could be implemented to reduce the mortality in severe EV71 cases.

The current study aims to investigate biomarkers which are associated with severity of EV71 infection in HFMD cases.

2. Methods

2.1. Study subjects and sample

All HFMD patients were recruited from the Nanjing Children's Hospital Affiliated to Nanjing Medical University in 2014 to 2015. HFMD patients were diagnosed according to the China Ministry of Health, 2010 version of the "Hand, Foot and Mouth Disease Diagnosis and Treatment Guidelines".[28] Throat swab and blood samples were collected upon diagnosis of HFMD. The types of enterovirus were tested by polymerase chain reaction (PCR) and was verified by presence of EV71 IgM antibody in blood sample. Only those who were EV71 positive were included in the current study. Patients were divided into severe HFMD (S) and control HFMD (C) based on the progression of the disease. Severe HFMD patients were those who presented with one or more conditions of the following central nervous system complications:

(1) aseptic meningitis,
(2) encephalitis.

Aseptic meningitis was confirmed based on examination of cerebrospinal fluid (CSF), WBC $>20 \times 10^6$/L with normal glucose level, normal or increased protein level (based on Zhu Futang Practice of Pediatrics 8th Edition Chinese Edition), and negative for Gram stain smear in addition to fever, vomiting, irritability, and other meningeal signs, without disturbed consciousness. Encephalitis was confirmed based on presence of WBC of $>20 \times 10^6$/L in CSF, disturbed consciousness and neurological signs. Control HFMD patients were defined as those who did not have central nervous system complications. Both groups had been ruled out merger other common infectious diseases, such as measles, cytomegalovirus infection, and mumps. This study was reviewed and approved by Institutional Ethics Committees of the Nanjing Children's Hospital Affiliated to Nanjing Medical University. Consents were obtained from parents of young patients.

2.2. Study design

All HFMD patients who were positive for EV71 were recruited for the study and categorized as severe HFMD or control HFMD based on presence or absence of central nervous system complications. In the discovery phase, genome-wide transcriptional analysis was performed in 10 severe HFMD patients and 10 control HFMD patients. The mRNA expression was analyzed using High-throughput RNA sequencing and the result was further verified by q-PCR. The gene with the highest expression level was selected as potential marker and was validated in an independent cohort.

2.3. Blood sample processing

Lithium heparin anticoagulant tubes were used to collect 5 ml peripheral blood from each volunteer. Samples were allowed to clot for 15 minutes at room temperature and then put on ice in a cooler and transported to the laboratory within 2 hours after collection. Tubes were centrifuged ($1000 \times g$ for 10 minutes) in a refrigerated centrifuge and serum was apportioned into 0.5 mL aliquots and stored at $-80°$C until further processing.

2.4. RNA extraction and quality control

RNA was extracted from serum using RNeasy Mini Kit (Qiagen, Germany) according to the kit instructions. The quality and concentration of RNA was detected using NanoDrop 2000 (Thermo, USA). Each of the RNA samples showed an A260: A230 ratio above 2.0 and an A260:A280 ratio above 1.8. RNA integrity was assessed using the Agilent 2200 Tape Station, a standard denaturing agarose gel electrophoresis and each sample had a RIN^e above 7.0.

2.5. High-throughput RNA sequencing and data analysis

High-throughput RNA sequencing was performed by Ribobio (Guangzhou, China). Briefly, total RNA was isolated from serums of the patients, then purified mRNA was fragmented in fragmentation buffer. We used these short fragments of mRNA as templates to synthesize the first-strand cDNA, using random hexamer primers. The second-strand cDNA was synthesized using buffer, dNTPs, RNase H, and DNA polymerase I, respectively. Following the purify double-stranded cDNAs and addition of a single A base, Illumina sequencing adaptors were ligated onto the short fragments. Constructed libraries were sequenced using Illumina HiSeq 2500, according to the manufacturer's instructions. The samples expression levels were presented as RPKM (expected number of Reads Per Kilobase of transcript sequence per Million base pairs sequenced). The gene-level RPKM values were normalized using the log2 values for further analyses. Differential expression was determined with log2 fold change more than 1 or less than -1, and P value $\leq$.05. The data is available upon request.

2.6. Quantitative real-time PCR

The mRNA expression was validated with SYBR Green qPCR assay and β-actin was considered as a house keeping gene. RNA was reversed transcribed into cDNA using PrimeScript^{TM} RT reagent Kit (Takara companies, Japan). The qPCR Primers used was shown in Table 2. Reaction conditions as follows: 95°C, 30 s; 95°C, 5 s, 60°C, 34 s, 40 cycles. The data were expressed as mRNA copy number relative to theβ-actin.

2.7. Statistical analysis

The data was analyzed using the SPSS version 19. Differential expression levels of mRNAs were compared by independent-samples t test among different groups. Relative expression values of SCARA3 were expressed as the mean ± standard deviation, and a P value of $<$.05 was considered statistically significant.

3. Results

A total of 110 HFMD patients who were positive for EV71 and had blood samples available were included in this study. Out of 110 patients, 55 who presented with central nervous system complications were classified as severe HFMD and 55 who did not have any central nervous system complications were classified as control HFMD (Table 1.). In the discovery phase, we performed genome-wide transcriptional analysis using the serum RNA isolated from 10 severe HFMD patients (S group) and 10 control HFMD patients (C group). Clustering analysis showed that 549 genes were differently expressed in S and C groups. There were 392 upregulated mRNAs and 157 downregulated mRNAs in S group compared to C group. A heat map of the 17 genes with the highest fold change of at least 3-fold was created

Table 1

Characteristics of HFMD patients.

	Severe group (n = 55)	Control group (n = 55)	P value
EV71 infection	100%	100%	–
Gender (male/female)	32:23	30:25	.848
Age (year)	1.97 ± 1.05	2.17 ± 1.24	.367
Duration of illness at sampling (hour)	36.56 ± 9.03	33.47 ± 10.06	.09
Fever	100% (55/55)	90.90% (50/55)	.057
Rash	96.36% (53/55)	100% (55/55)	.495
Oral ulcer	90.90% (50/55)	94.54% (52/55)	.716
Vomiting	14.54% (8/55)	5.45% (3/55)	.202
Convulsion	10.90% (6/55)	3.63% (2/55)	.271
Lethargy	54.54% (30/55)	0% (0/55)	<.001
Mean white blood cell (/mm3) ± SD	17.80 ± 1.79	7.03 ± 1.70	<.001
Blood glucose level (mmol/L) ± SD	9.64 ± 0.90	5.32 ± 1.14	<.001

HFMD = hand foot mouth disease.

(Fig. 1). Among 17 significant differentially expressed genes, 16 of them were upregulated while 1 mRNA was downregulated.

To verify the data from RNA sequencing, the 15 mRNA were validated using qPCR. The results showed the expression patterns of those mRNA were consistent with sequencing data. SCARA3 was the highest upregulated gene in the severe patients compared to controls (Fig. 2).

SCARA3 was selected as a potential biomarker for validation because of the highest expression level among all significantly expressed mRNA. The expression level of SCARA3 were assessed in independent cohort comprising 45 severe HFMD patients and 45 control HFMD patients using qPCR assay. The mean relative expression levels in severe HFMD and control HFMD patients were 10.1-fold and 5.0-fold, respectively, P value <.001 (Fig. 3).

4. Discussion

In this study, we first compared the different mRNA expression of severe patients group with control group in EV71 patients by High-throughput RNA sequencing. Sixteen genes were upregulated and 1 gene was downregulated in severe HFMD patients compared with control group. We further verified this result by q-PCR and found that the expression of SCARA3 was the most significantly increased in severe HFMD patients. SCARA3 was selected as potential prognostic marker and was validated in an independent cohort. The mean value of SCARA3 expression was 2 times higher in severe EV71 patients than that in control group. It suggested the upregulation of SCARA3 may be an indication of

Table 2

List of primers used in the study.

| Primer name	Forward	Revers
CASQ2	5′- CTGAGCATCCTGTGGATCG-3′	5′- TCTTCTCCCAGTAGGCAACG -3′
TFPI2	5′-TTTCGTATAAAGCGGGTATT -3′	5′-ACGACCCGCTAAACAAAAC -3′
USP46	5′-GAACCTTCCCTAGAGGGAATAC-3′	5′- CTGTCTTGTCAAGCATTCTAGG-3′
SLC46A3	5′-CTAACAGGACTGTCATCTGGC-3′	5′-CATAGTAACATTCTGAGATG-3′
GUSB	5′- CTGTACACGACACCCACCAC-3′	5′- ATTCGCCACGACTTTGTT-3′
SAMD4B	5′-TCGGAGTACATGAGGCTACTGC-3′	5′-AGGGCCAGTGCGTTGCGGTC-3′
ZNF44	5′-TCATCCCTGAATTGCTACAT-3′	5′-GCGATAACTTAAGCCTT-3′
ANTXR1	5′TGCAACACAGAAATGCTCTGCCTG-3′	5′-TTTATCCCTGGGTGATGAAGCCCA-3′
SCARA3	5′- TGCAGCTGGATAACATCTCG-3′	5′- CTTGGTCATCCTGGGCTTTA-3′
TTN	5′-GGCCTTTCAATTGCCTGGT-3′	5′-TCGGCTTCTATTGGTGAAGG-3′
RWDD1	5′- GGAGTCCATCTACCCTGACTCC-3′	5′-CTGATAATACTTAGCAGGACCT-3′
HELLS	5′-GGTGAGTGTCCAGGCATGCC-3′	5′-CCAAGAGTTCTGCATCAAAC-3′
GABRB2	5′-TCTGAAGTCAATATGGATTA-3′	5′-GGTTCTTAACAGTCACTCCG-3′
FARP2	5′-GATGGCCAGGTATTACTGAC-3′	5′-GAAGCACCACATTCTTTGGC-3′
FAM181B	5′-TGCGCGAGGCCACCCGCGAT-3′	5′-CGGCCGTTTGGCTGGCGTGT-3′
β-actin	5′- AGATGTGGATCAGCAAGCAG-3′	5′-GCGCAAGTTAGGTTTTGTCA-3′
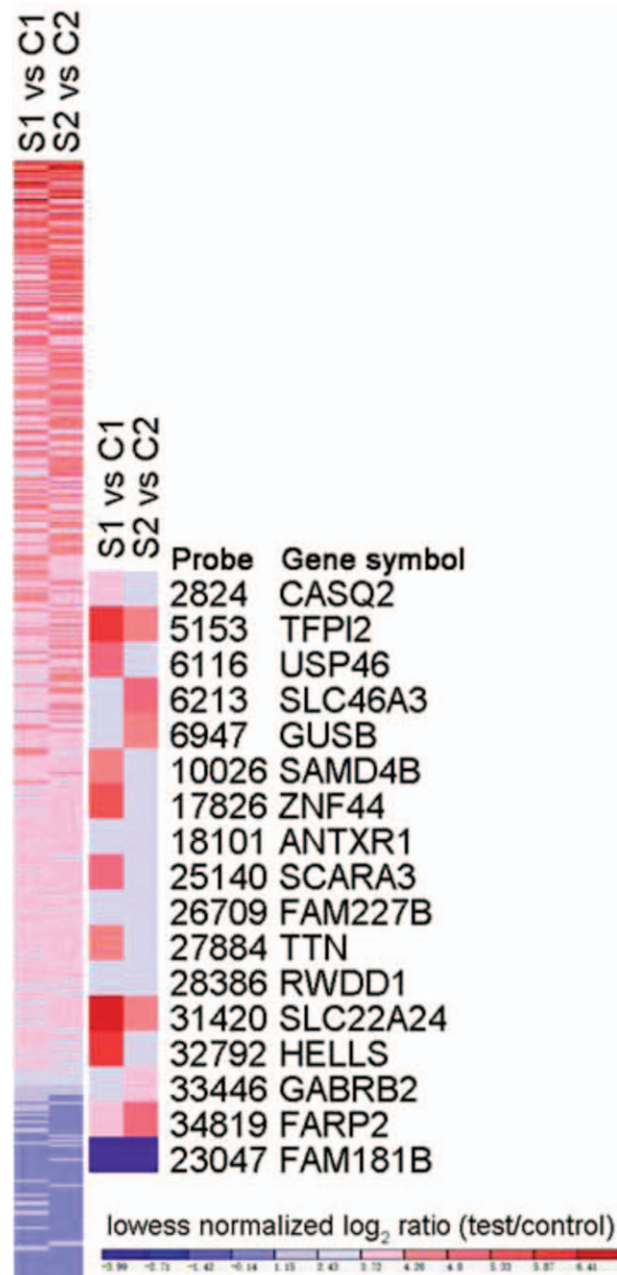
Figure 1. High-throughput RNA sequencing of severe HFMD patients and control HFMD patients. Heat map of the high-throughput RNA sequencing data obtained for severe patients and control patients. Blue color refers to downregulation; red color refers to upregulation. HFMD = hand foot mouth disease.

progression of EV71 infection in HFMD. Our report is the first to show the association between SCARA3 and the severity of EV71 infection.

The class A scavenger receptors (SCARAs) are a family of cell surface glycoproteins and involved in the uptake of nucleic acids,
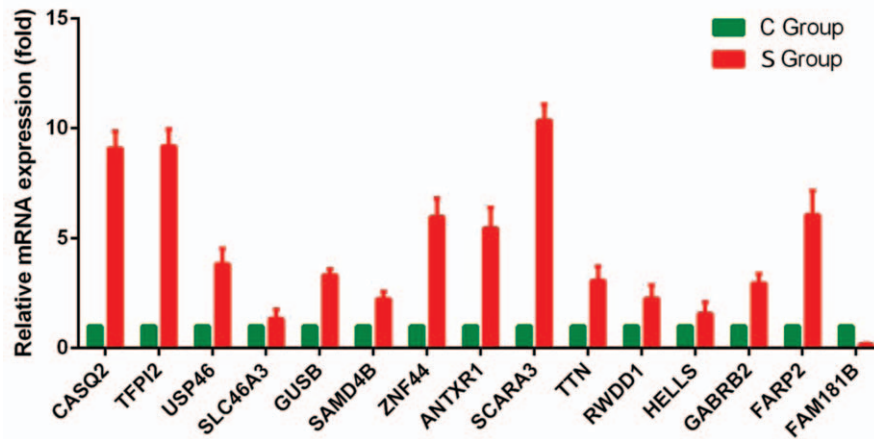
Figure 2. Validation of the expression of significantly upregulated and downregulated genes between S group and C group. The genes mRNA levels were verified using qPCR in serum from severe patients (n=10) and control patients (n=10). The expression of mRNA was 2−ΔΔCt relative to β-actin.

double-stranded RNA, and oligonucleotide. There are 5 members have been identified in scavenger receptor family: SR-AI/II/III, MARCO, SCARA3, SCARA4, and SCARA5.[29–31] SCARAs have a vital roles in the immune response against bacterial and viral pathogens,[32–34] such as the increased expression of SCARA5 involved in the cancer metastatic progression, and MARCO plays an important role in bacteria-binding innate immune response.[31,35] As for SCARA3, its expression could be altered by oxidative stress, also functioned as a cellular stress response gene to scavenge reactive oxygen species (ROS) and other harmful products of oxidation. Moreover, SCARA3 can acquire fatty acids by binding to polyanionic ligands and representing a major route through dendritic cells and macrophages in cancers.[36,37] It seemed the progression of EV71 infection had stimulated the immune system and caused the overexpression of SCARA3. Animal studies on how the EV71 infection activates secretion of SCARA3 will be helpful.

There is no specific antiviral medications or effective vaccine for EV71. The severe cases can progress quickly and the current treatment is largely supportive. SCARA3 could be used as prognostic marker to identify severe cases. Continuous electro-cardiogram monitoring and early intervention such as treatment with vasoactive drugs, Gamma globulin or Glucocorticoid in those severe EV71 infection cases could help reduce the mortality. Although the level of SCARA3 expression in severe EV71 patients was statistically significantly higher than that in control group (P < .001, Fig. 3), there were some overlaps between severe group and control group. This suggested SCARA3 should be used carefully together with observation of patient symptoms.

The study has some limitations. The sample size of validation cohort was small. Although there were 17 significant differentially expressed genes, only SCARA3 was selected for validation because of budget constrain. Lastly, the SCARA3 expression level was not measured after patient with severe EV71 infection recovered to verify its use as prognostic effect.

In conclusion, we found the expression of SCARA3 was increased in severe HFMD patients compared with the control patients, indicating that SCARA3 was associated with the severity of HFMD. Our study suggested that SCARA3 may participate in the progression of HFMD and could serve as a potential prognostic indicator in HFMD. The result is required to be validated in a prospective study before it can be used as prognostic marker in clinic. More work is needed to understand the molecular mechanism of SCARA3 in EV71 infection.

Author contributions

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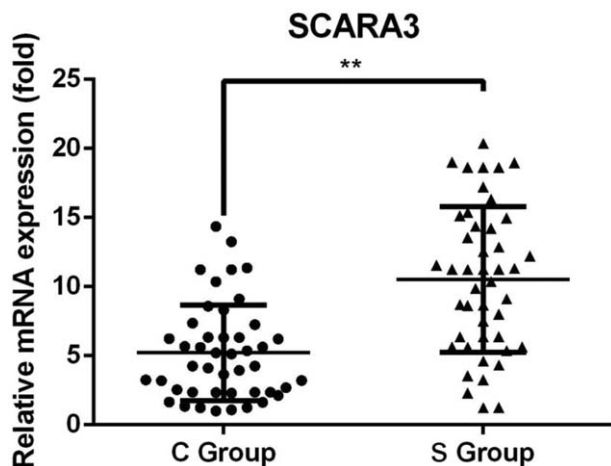

Figure 3. SCARA3 is associated with severity of hand foot mouth disease. Comparing differences in the mRNA expression levels of SCARA3 between severe patients (n=45) and control patients (n=45). β-actin was used as an internal control. P < 0.001. SCARA3 = Scavenger receptor class A, member 3.

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