Journal of Dermatological Science 95 (2019) 70–75

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

Original Article

Serum squamous cell carcinoma antigen (SCCA)-2 correlates with clinical severity of pediatric atopic dermatitis in Ishigaki cohort

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ARTICLE INFO

Article history:
Received 4 July 2019
Received in revised form 10 July 2019
Accepted 10 July 2019

Keywords:
Atopic dermatitis
Pediatric
Squamous cell carcinoma antigen
TARC
Th2

ABSTRACT

Background: We sometimes encounter difficulties in assessing the severity of pediatric atopic dermatitis (AD) using currently available biomarkers such as thymus and activation-regulated chemokine (TARC) due to the higher baseline values in non-AD children. Recent case control studies have indicated the usefulness of squamous cell carcinoma antigens (SCCAs) in pediatric and adult AD. Notably, SCCAs are induced by IL-4 and IL-13, vital Th2 cytokines that play important roles in AD etiology.
Objectives: Relatively low prevalence and mild disease severity of pediatric AD are observed in our Ishigaki cohort presumably due to the moisturising subtropical climate, which could conversely mean possible higher allergic potential of non-AD subjects towards AD. Thus, the purpose of this study was to further investigate the feasibility of using SCCAs together with TARC and periostin as biomarkers for pediatric AD even in the Ishigaki cohort.
Methods: We enrolled 1459 nursery school children and identified 96 as having AD through 2009–2011. As statistical analyses, we performed Student's *t*-test, correlation analysis, and receiver and operating characteristic (ROC) analysis.
Results: Serum SCCA1, SCCA2, periostin and TARC levels were all significantly increased in AD compared with those in non-AD, but only serum SCCA2 showed a significant increase in AD when assessed in each age group or in subgroup analysis. Among the biomarkers tested, serum SCCA2 also showed the best correlations with clinical AD severity and TARC and showed the best diagnosability for AD in ROC analysis.
Conclusions: SCCA2 is a potent biomarker for pediatric AD in the Ishigaki cohort.

1. Introduction

Several biomarkers have been found to be useful for assessing the severity of atopic dermatitis (AD), such as thymus and activation-regulated chemokine (TARC) [1] and macrophage-derived chemokine [2]. TARC has been used as a biomarker for AD under the Japanese national insurance system since 2008. The use of such accredited objective biomarkers helps to maintain patients' motivation to undergo treatment and reduces their fears about possible overtreatment. This is particularly important for topical corticosteroids, as their unwelcome adverse events (e.g. skin atrophy) have been a major concern for AD patients [3].

However, we sometimes encounter difficulties in assessing the severity of pediatric AD using currently available biomarkers such as TARC due to the higher baseline values of these biomarkers in non-AD children [4,5] compared with those in adults. Several case-control studies have indicated the usefulness of squamous cell carcinoma antigens (SCCAs) that are induced by IL-4 and IL-13 [6] in pediatric [7,8] and adult AD [9] and the biomarker might possibly solve such a problem. Incidentally, relatively low prevalence [4] of pediatric AD has been reported in our Ishigaki cohort presumably due to the moisturising subtropical climate [10], which could conversely mean higher allergic potential of non-AD subjects [11] possibly towards AD in the cohort.

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https://doi.org/10.1016/j.jdermsci.2019.07.005
0923-1811/

Thus, the purpose of this study was to further investigate the feasibility of using other AD biomarkers including squamous cell carcinoma antigens (SCCAs) for pediatric AD even in the Ishigaki cohort.

2. Participants and methods

In this study, we enrolled 1459 nursery school infants and children from the 2009 to 2011 examinations in the Ishigaki island population-based cohort and identified 96 individuals with AD according to the Japanese Dermatological Association on AD [12]. The sex ratio of the participants was as follows: female/male/no data = 716 (49.1%)/741 (50.8%)/2 (0.1%). The subjects were aged from 0 to 6 years old; the age distribution is shown in Table 1. The participants were asked to complete a questionnaire and undergo dermatological and blood examinations, as previously described [4]. The serum levels of SCCA1, SCCA2, periostin [13] and TARC were measured using sera of these enrolled children. This study was approved by the ethics committee of Kyushu University (#270-07).

3. Statistical analysis

For statistical analysis, Student's *t*-test was performed with Bonferroni correction using Microsoft Excel 2013 (Microsoft Corp., Redmond, WA, USA), and relation analysis and receiver and operating characteristic (ROC) analysis were conducted using GraphPad Prism 5.02 (GraphPad Software, San Diego, CA, USA) and IBM SPSS Statistics Ver. 25 (IBM Japan, Tokyo, Japan), respectively. $P < 0.05$ was considered to indicate a statistically significant difference.

4. Results

4.1. Prevalence of AD and its severity

Excluding seven subjects for whom no data from dermatology examinations were available, we identified 96 children with AD from among 1452 nursery school children (point prevalence: 6.6%). The sex ratio and age distribution of the children are shown in Table 1. No children with AD were aged 0 or 6. The disease severity of the 96 children with AD according to the criteria on AD severity as presented by the Japanese Ministry of Health, Labour and Welfare (MHLW) research group [8] was as follows: mild: 88 (91.7%), moderate: 6 (6.3%), severe: 0 (0.0%) and no data available: 2 (2.1%) (Table 1).

Table 1
The background of the subjects in this study.

Age distribution

Age	0	1	2	3	4	5	6	No data
AD	0	9	20	21	28	18	0	0
Non-AD	4	144	253	376	387	168	23	1
No data on AD exam.	0	0	3	2	1	1	0	0
Total	4	153	276	399	416	187	23	1

Sex

Sex	Boys	Girls	No data
AD	46	50	0
Non-AD	690	664	2
No data on AD exam.	5	2	0
Total	741	716	2

Disease severity (AD)

Severity[a]	Mild	Moderate	Severe	Most severe	No data
Number	88	6	0	0	2

[a] Severity according to the Japanese MHLW research group criteria.

4.2. Serum SCCA2 as an AD biomarker

The levels of serum SCCA1, SCCA2, periostin and TARC were all significantly increased in children with AD compared with the levels in children without AD (Fig. 1). There was no sex difference in the levels of these biomarkers in children both with and without AD (Suppl. Fig. 1). Among these tested markers, only serum SCCA2 showed a significant increase in children with AD in each age group (Fig. 2), for the groups in which there were children with AD. We then subcategorized the children with and without AD in terms of whether they had a history of asthma, since some of these biomarkers are reportedly associated with asthma [14,15]. There were no biomarkers to differentiate asthma

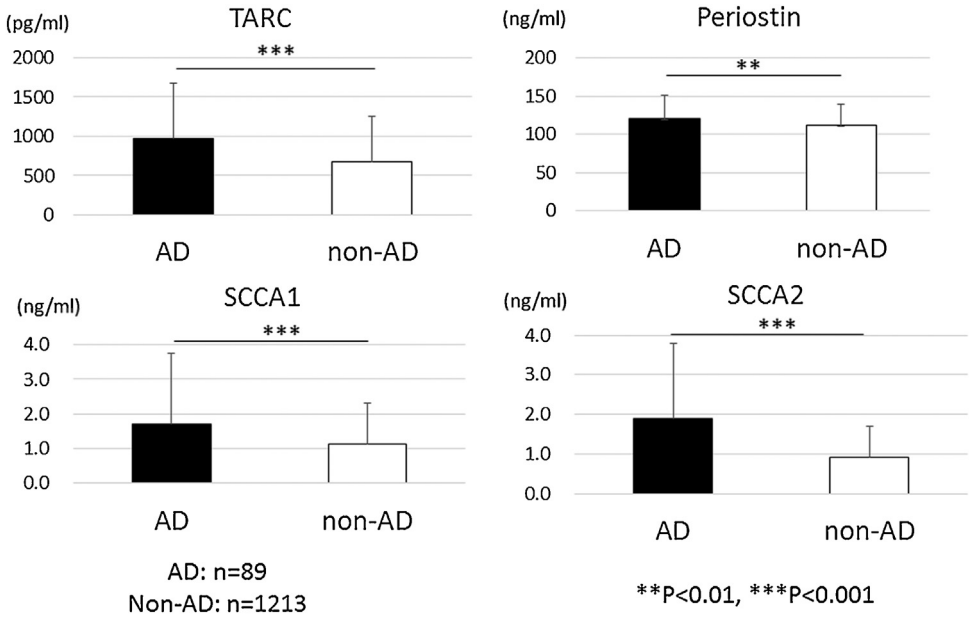

Fig. 1. Serum TARC, periostin, SCCA1 and SCCA2 as biomarkers for AD.
Serum TARC, periostin, SCCA1 and SCCA2 were significantly increased in pediatric AD.

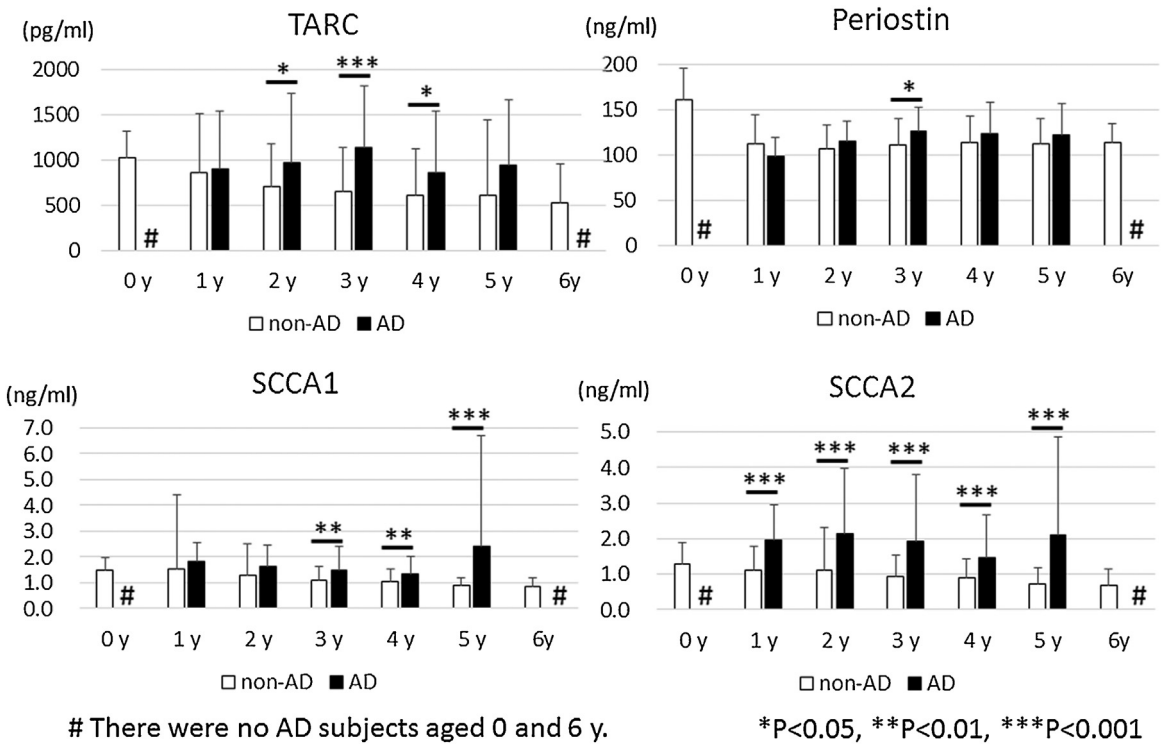

Fig. 2. Serum TARC, periostin, SCCA1 and SCCA2 as biomarkers for AD in each age group.
Only serum SCCA2 was significantly increased in pediatric patients with AD at the different ages.

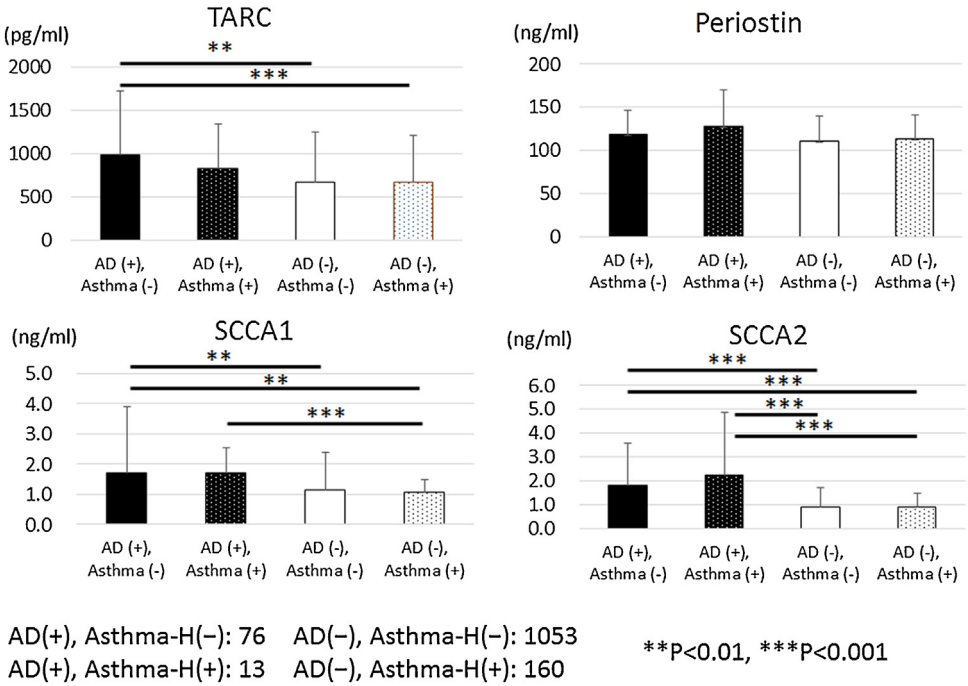

Fig. 3. Serum TARC, periostin, SCCA1 and SCCA2 as biomarkers for AD when subdivided by history of asthma.
Serum SCCA2 was significantly increased in pediatric AD subdivided by a history of asthma.

history in children either with or without AD, but again only serum SCCA2 showed a significant increase in the AD subgroups in this subanalysis (Fig. 3), while other biomarkers, including TARC, failed to do so.

Serum SCCA2 correlated well with AD severity as assessed by the Japanese MHLW research group criteria (Fig. 4). Serum SCCA2 also showed a higher correlation (r = 0.41) with TARC, a representative biomarker of AD severity, in children with AD,

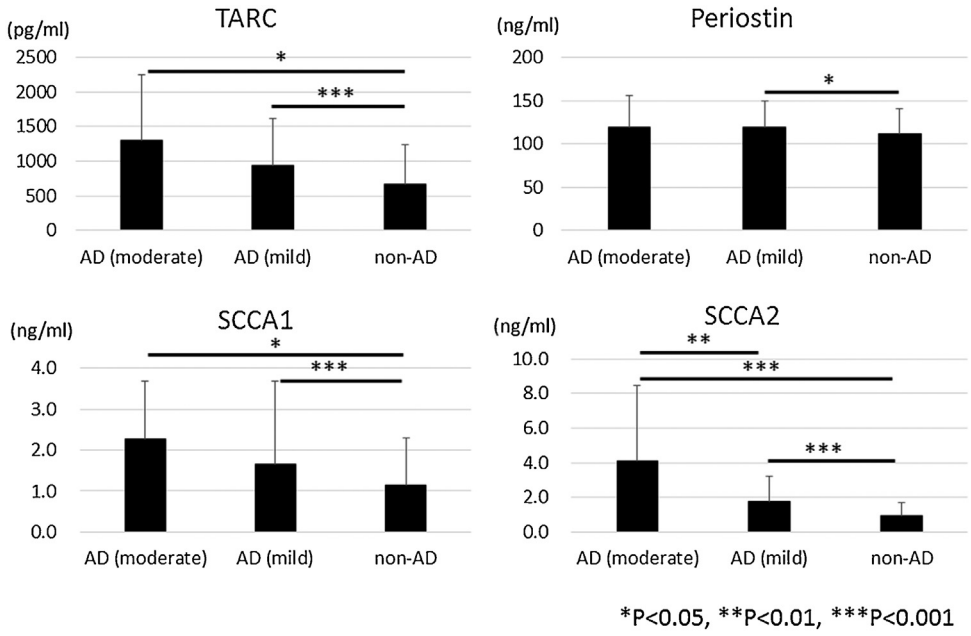

Fig. 4. Correlations of serum TARC, periostin, SCCA1 and SCCA2 with disease severity of AD.
Serum SCCA2 correlated well with clinical disease severity in pediatric AD compared with other biomarkers.

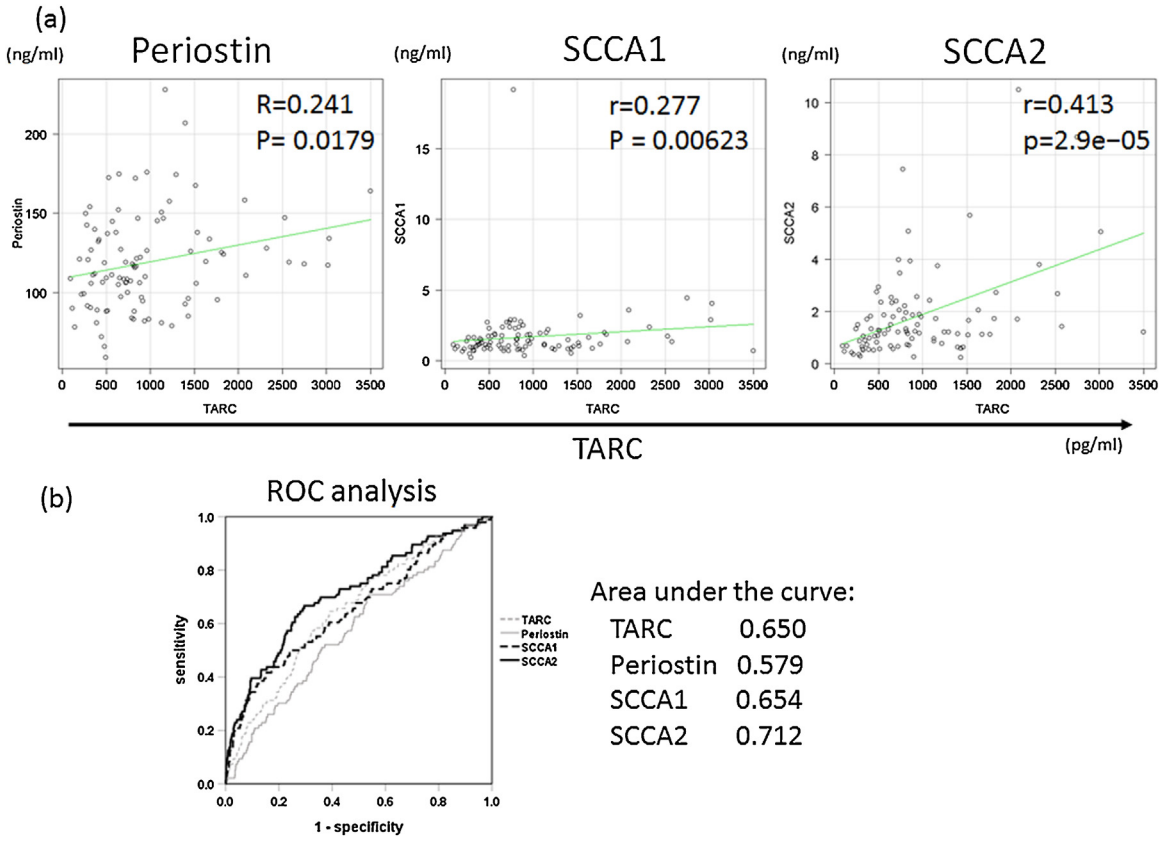

Fig. 5. Correlations and diagnosability of serum periostin, SCCA1, SCCA2 and serum TARC.
Serum SCCA2 shows the highest correlation with TARC, a currently available disease severity marker, in pediatric AD (a). Serum SCCA2 showed the best diagnosability for pediatric AD in ROC analysis among the biomarkers tested (b).

compared with SCCA1 (r = 0.28) and periostin (r = 0.24) (Fig. 5a). In addition, serum SCCA2 showed the highest diagnosability for AD in ROC analysis (area under the curve = 0.71) among the biomarkers tested in this study (Fig. 5b).

5. Discussion

Reliable AD biomarkers would help to avoid the burden of blood collection, especially from infants and young children. However, currently available AD biomarkers such as TARC are unfortunately

insufficiently sensitive to distinguish and evaluate pediatric AD because of their higher baseline values in children without AD compared with those of adolescents or adults. SCCA2 is an emerging biomarker for skin inflammatory diseases [16] and has been shown feasible for pediatric AD in several case-control study settings [7,8]. Then, our next question was whether such apparently potent AD biomarker was practically effective in evaluating severity and diagnosibirity of pediatric AD in the Ishigaki cohort in which low AD prevalence had been shown [4,10] and AD children with mild severity were dominant (Table 1). In the present study, we found that serum TARC, periostin, SCCA1 and SCCA2 were all significantly increased in pediatric AD without differing between these sexes, but biomarkers other than SCCA2 had limited power to significantly differentiate between children with and without AD in several examination settings. Serum SCCA2 appears to be the best biomarker among those tested as it showed a significant increase in AD with age and in other subgroup analyses.

There happened to be no children with AD aged 0 and 6, presumably due to the relatively small numbers of subjects at these ages. Only infants aged >6 months are allowed to enter nursery schools in Japan and some children aged 5–6 also start to go to kindergarten rather than nursery school, for the diverse educational opportunities. Furthermore, the timing of the examination (July to September) and the Japanese fiscal year (starting in April), which affect entering and leaving nursery schools, might also have affected the relatively small numbers of subjects at these ages.

Serum SCCA2 correlated well with both disease severity and an accredited biomarker, TARC, in pediatric AD. Furthermore, serum SCCA2 showed the highest diagnosability for AD in infants and young children among the biomarkers tested.

SCCAs have been shown to be induced by IL-4 and IL-13 [6,17], the vital Th2 cytokines that play important roles in AD etiology [18,19]. Indeed, biologic or molecular therapies targeting the cytokine receptor [20] or its downstream signals [21,22] are now clinically available or under clinical trials and appear to have considerable therapeutic effects, improving patient quality of life as well as AD symptoms [23]. SCCAs may therefore be a good and simple surrogate marker for AD severity in this context.

Alternatively, SCCAs might reflect AD and its severity in other ways. Although both SCCA1 and SCCA2 are regulated by IL-4 and IL-13 and show 92% homology [24], they have distinct properties. SCCA2 works as a serine protease inhibitor that inhibits chymotrypsin-like proteinases such as cathepsin G and mast cell chymase, while SCCA1 inhibits papain-like cysteine proteinases [25]. Mast cell chymase is increased in AD [26] and a chymase inhibitor has been shown to improve dermatitis of AD model mice [27]. SCCA2 was also shown to inhibit cysteine protease activity of a major mite allergen, Der p1 [28]. Thus, SCCA2 might be induced to alleviate the skin inflammation of AD, eventually reflecting the degree of AD severity. The present findings suggest that SCCA2 plays a more crucial role in this than SCCA1.

The limitation of the study is the relatively small number of sample size and that the present study was conducted in a Japanese population as this is an island population-based cohort which might potentially cause ethnic bias. Therefore, studies examining the feasibility of SCCA2 in AD children of other countries/ethnics are awaited. However, a good correlation of SCCA2 with an accredited AD biomarker TARC or with a disease severity score in the present study and promising results from other studies examining the feasibility of SCCA2 in AD children from other Japanese areas (Mie, Tokyo and Fukuoka) [8] or AD adults from Yokohama area [9] may support the generalisability of this biomarker.

In conclusion, serum SCCA2 may be a potent biomarker for pediatric AD and is potentially applicable for screening for AD in medical check-ups of infants.

Funding sources

This work was financially supported by a research grant from the Ministry of Health, Labour and Welfare, Japan (#H23-Immunology-Genaral-008).

Declaration of Competing Interest

Junya Ono and Yoshinori Azuma are employees of Shino-Test Corporation.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdermsci.2019.07.005.

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