

Angiotensin-converting enzyme II expression and its implication in the association between COVID-19 and allergic rhinitis

To the Editor:

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affects more than 17 million of people and results in more than 666 000 deaths all over the world. Although allergic diseases are highly prevalent globally, their risks for the development of COVID-19 remain poorly understood.

Severe acute respiratory syndrome coronavirus 2 entry host cells via angiotensin-converting enzyme II (ACE2).¹ Upregulated ACE2 expression has been associated with increased risk of COVID-19 in patients with chronic obstructive pulmonary disease, diabetes, and hypertension.² ACE2 gene expression is enriched in nasal epithelial cells, highlighting the importance of nose as a portal for initial SARS-CoV-2 infection and transmission.

Allergic rhinitis (AR) is the most common disorder of nose and affects 10%-40% of the population.³ Previous studies reported low incidences of AR in COVID-19 patients, ranging from 0% to 1.8% in China.^{4,5} However, those results were generated solely based on the medical records, and AR comorbidity might not be well considered under actual emergency situation.^{4,5} Moreover, the association between AR comorbidity and the disease severity of COVID-19 and the role of ACE2 in this association are largely unknown.

Here, we retrospectively analyzed 1172 etiologically confirmed COVID-19 patients discharged from Tongji Hospital, Wuhan, China from January 27, 2020 to March 10, 2020. Hospital electronic medical records were extracted and comorbidities were reevaluated by the telephone follow-up. Both multivariate logistic regression and propensity score matching (PSM) analysis were performed to exclude the influence of potential confounding variables. In addition, repository inferior turbinate tissues and cells from 29 control subjects without AR and 29 patients with AR undergoing nasal septoplasty and collected before COVID-19 era were used for the study of ACE2 expression. Human nasal epithelial cells (HNECs) were collected by epithelial scrapings of the inferior turbinates from subjects without AR. Primary HNECs were cultured with the air-liquid interface method. The cell culture was also performed before COVID-19 era, and the ACE2 expression was analyzed in this study. The

RNA-seq data of nasal and bronchial brushings from 7 patients with concomitant AR and asthma and 9 healthy controls were acquired from the Gene Expression Omnibus database (GSE101720). More information regarding subjects and methods is provided in this article's Online Supplement including Tables S1-S2.

In our cohort, 115 (9.8%) patients reported physician-diagnosed AR. COVID-19 patients without AR were older than those with AR (61 [49-69] vs 54 [40-65]; $P < .01$). Patients with AR had a higher incidence of concomitant chronic liver disease (4.4% vs 1.1%; $P = .02$), and tended to have a higher incidence of asthma comorbidity (5.2% vs 2.2%; $P = .06$) and a lower incidence of hypertension (24.4% vs 32.5%; $P = .07$) than those without AR (Table S3). After adjusting for or propensity score matching for confounding factors, including age, gender, smoking status, and comorbidities (Table S3), no significant difference in frequencies of symptoms or laboratory results was found between COVID-19 patients with and without AR (Table 1 and Table S4). Importantly, no difference in the frequencies of severe cases on admission, receiving mechanical ventilation and other treatments, or complications including severe acute respiratory syndrome was revealed for patients with and without AR either (Table 1). In PSM analysis, we were able to match 109 patients without AR to 109 patients with AR at a ratio of 1:1 (Table S3).

We next studied ACE2 expression and found its mRNA and protein expression in nasal tissues was comparable between AR patients and control subjects (Figure 1A,B). ACE2 mRNA expression was downregulated by IL-4 and IL-13, whereas upregulated by IFN- α , IFN- γ , and TNF- α in cultured HNECs (Figure 1C). We discovered that the mRNA expression of type 2 response genes, including *ST6GAL1*, *POSTN*, and *CCL26*, was increased in nasal tissues in AR patients compared with that in non-AR controls, however, the mRNA expression of IFN response genes, including *CXCL10* and *CXCL11*, was comparable between AR patients and non-AR controls (Figure S1). ACE2 expression positively correlated with the expression of IFN response genes, but not type 2 response genes, in nasal tissues when analyzing AR and control subjects together or separately (Figure 1D-E and Figure S2). Our findings of ACE2 expression in nasal tissues in AR patients and its relationship with the expression of IFN response genes were confirmed in nasal brushing cells from patients with concomitant AR and asthma by analyzing the public database (GSE101720) (Figures S3 and S4).

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TABLE 1 Clinical characteristics, complications, and treatments of COVID-19 patients without and with AR before and after propensity score matching

Characteristics	Unmatched		P value	Adjusted P value ^a	Matched (1:1) ^a		
	Without AR	With AR			Without AR	With AR	P value
Subject, N	1057	115	-	-	109	109	-
Systemic signs and symptoms, N (%)	-	-	-	-	-	-	-
Fever	823 (77.9)	98 (85.2)	.07	.09	85 (78.0)	95 (87.2)	.10
Cough	700 (66.2)	67 (58.3)	.09	.08	73 (67.0)	62 (56.9)	.16
Shortness of breath	455 (43.1)	40 (34.8)	.09	.07	52 (47.7)	38 (34.9)	.07
Fatigue	261 (24.7)	24 (20.9)	.36	.43	30 (27.5)	22 (20.2)	.27
Anorexia	253 (23.9)	21 (18.3)	.17	.09	26 (23.9)	19 (17.4)	.32
Diarrhea	182 (17.2)	24 (20.9)	.33	.42	16 (14.7)	21 (19.3)	.47
Myalgia	157 (14.9)	15 (13.0)	.60	.62	18 (16.5)	12 (11.0)	.33
Nausea and vomiting	78 (7.4)	7 (6.1)	.61	.55	5 (4.6)	5 (4.6)	.99
Headache	78 (7.4)	9 (7.8)	.86	.94	13 (11.9)	9 (8.3)	.50
Dizziness	47 (4.5)	5 (4.4)	.96	.99	3 (2.8)	5 (4.6)	.72
Severe COVID-19 cases, N (%)	183 (17.3)	16 (13.9)	.36	.79	17 (15.6)	16 (14.7)	.99
Complications, N (%)	-	-	-	-	-	-	-
Acute liver injury	70 (6.6)	9 (7.8)	.56	.68	6 (5.5)	7 (6.4)	.99
ARDS	64 (6.1)	5 (4.3)	.44	.57	5 (4.6)	5 (4.6)	.99
Acute kidney injury	61 (5.8)	2 (1.7)	.08	.28	3 (2.8)	2 (1.8)	.99
Acute myocardial injury	30 (2.8)	1 (0.9)	.35	.29	3 (2.8)	1 (0.9)	.62
Shock	7 (0.7)	2 (1.7)	.21	.38	0 (0)	2 (1.8)	.50
In-hospital treatments, N (%)	-	-	-	-	-	-	-
Oxygen supplementation	844 (79.9)	85 (73.9)	.14	.29	87 (79.8)	79 (72.5)	.27
Mechanical ventilation	41 (3.9)	3 (2.6)	.48	.66	4 (3.7)	3 (2.8)	.99
Antibiotic treatment	766 (72.5)	84 (73.0)	.90	.73	83 (76.1)	79 (72.5)	.64
Antiviral treatment	985 (93.2)	107 (93.0)	.95	.99	102 (93.6)	101 (92.7)	.99
Glucocorticoid therapy	273 (25.8)	22 (19.1)	.12	.06	32 (29.4)	20 (18.3)	.08
Intravenous immunoglobulin therapy	171 (16.2)	18 (15.7)	.88	.96	19 (17.4)	16 (14.7)	.71

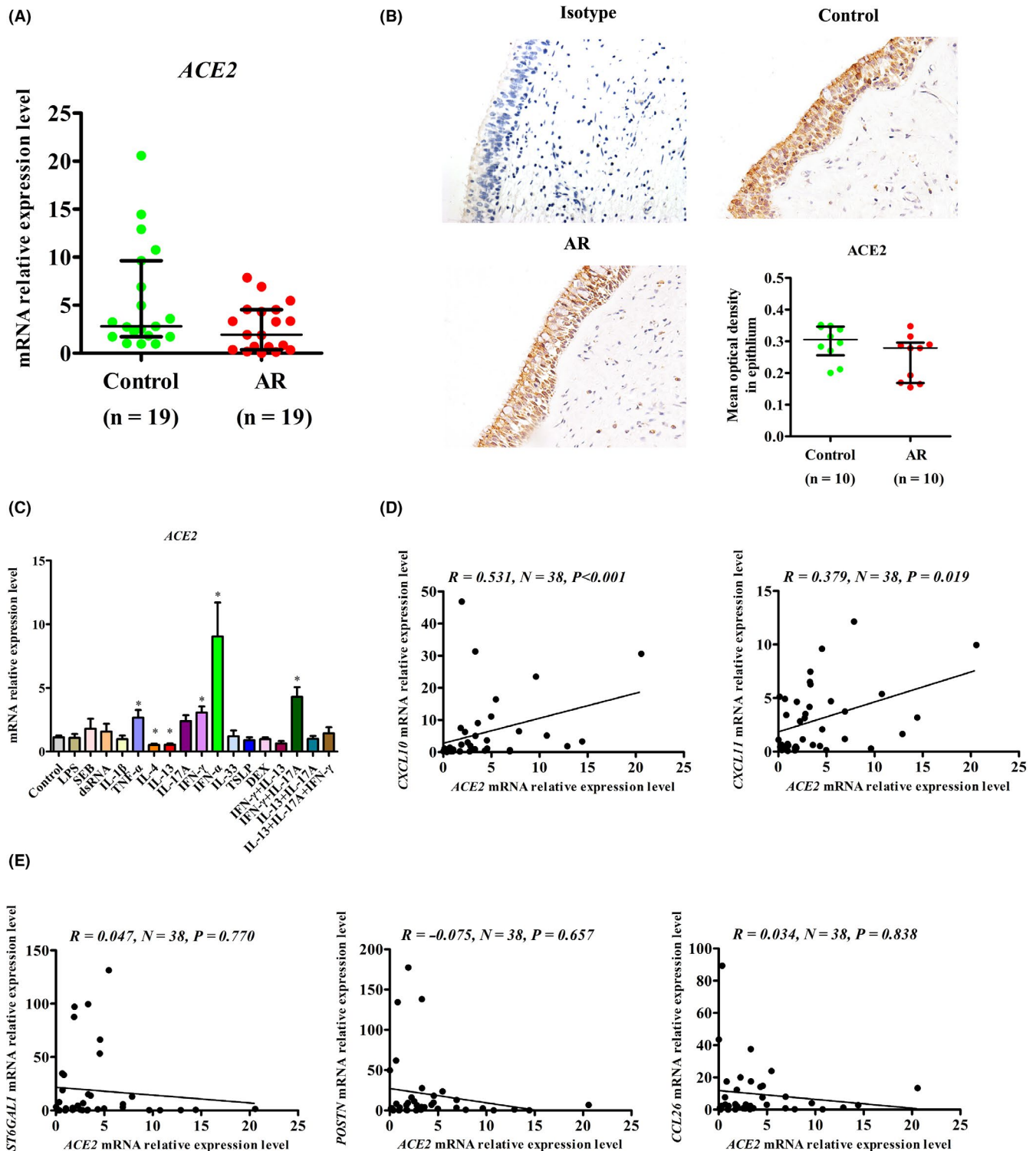
Note: Data are presented numbers with percentages for categorical variables.

For categorical variables, Chi-square or Fisher's exact test was applied to compare the difference in proportions between groups when appropriate. Abbreviations: AR, allergic rhinitis; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019.

^aAge, gender, smoking status, and all comorbidities were selected for propensity score matching. Please see Table S3.

*In adjusted logistic regression analysis, adjusted variables included age, gender, smoking, and comorbidities (hypertension, diabetes, cardiovascular disease cerebrovascular diseases, malignancy, chronic liver diseases, chronic kidney diseases, chronic rhinosinusitis, asthma, and chronic obstructive pulmonary disease).

FIGURE 1 Angiotensin-converting enzyme II expression and its correlation with IFN and type 2 response in AR patients and healthy controls. A, The mRNA expression level of ACE2 gene in inferior turbinate tissues from AR patients and controls as detected by quantitative RT-PCR. Control, n = 19; AR, n = 19. B, Immunohistochemistry study of ACE2 expression in inferior turbinate tissues from AR patients and controls. The representative photomicrographs are shown (original magnification $\times 400$). The staining intensity in epithelium was quantified, and the results were presented as average optical density value per unit area. Control, n = 10; AR, n = 10. C, Human nasal epithelial cells (HNECs) scraped from inferior turbinate mucosa of control subjects were cultured with an air-liquid interface method. After differentiation, HNECs were stimulated with various cytokines, dexamethasone (DEX), poly (I:C) (dsRNA), lipopolysaccharides (LPS), and staphylococcal enterotoxin B (SEB) for 6 h. After stimulation, cells were harvested for quantitative RT-PCR assay (n = 6). D and E, ACE2 mRNA expression positively correlated with the mRNA expression of IFN response genes (CXCL10 and CXCL11) (D), but not type 2 response genes (ST6GAL1, POSTN, and CCL26 expression) (E) in tissues when analyzing AR patients and control subjects together (n = 38). Tissue data are expressed as medians and interquartile ranges and analyzed by Mann-Whitney U 2-tailed test. Cell culture data are expressed as medians $\pm$ SEM and analyzed by unpaired Student's t test. Spearman's correlation was used for correlation analysis. ACE2, angiotensin-converting enzyme II; AR, allergic rhinitis; IL, interleukin; TNF- α , tumor necrosis factor (TNF) α ; IFN, interferon; TSLP, thymic stromal lymphopoietin; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; ST6GAL1, beta-galactoside alpha-2,6-sialyltransferase 1; POSTN, periostin



In contrast to nasal epithelial cells, *ACE2* gene expression was decreased in bronchial epithelial cells in patients with concomitant AR and allergic asthma as compared to that in healthy controls by analyzing GSE101720 datasheet (Figure S5A). *ACE2* gene expression negatively correlated with the expression of type 2 response genes (*POSTN*, *CLCA1*, and *IL1RL1*), but not IFN response genes (*IFI6*, *CXCL10*, and *CXCL11*) in bronchial epithelial cells when analyzing all the subjects or patients with asthma and AR alone (Figure S5B and Figure S6). We

further found nasal epithelial cells had higher *ACE2* and *CXCL10* expression levels, but lower *POSTN*, *CLCA1*, *CPA3*, and *IL1RL1* expression compared with those in bronchial epithelial cells (Figure S7A) in patients with concomitant AR and asthma. Consistently, the gene expression ratios of *CXCL10*/*ST6GAL1*, *CXCL10*/*POSTN*, *CXCL10*/*CPA3*, and *CXCL10*/*IL1RL1* were higher in nasal epithelial cells than in bronchial epithelial cells (Figure S7B), suggesting a predominant IFN and type 2 response in upper and lower airways, respectively, under allergic condition.

In this study, we carefully confirmed and reevaluated AR comorbidity in discharged COVID-19 patients by telephone follow-up. This may be the reason that the AR prevalence in our cohort (9.8%) was higher than those previously reported in Chinese COVID-19 patients (0%–1.8%).^{4,5} The prevalence of AR in our COVID-19 cohort is comparable to that in general populations in Wuhan (9.7%).⁶ In addition, we did not find any association between AR comorbidity and disease severity in COVID-19 patients. Chhiba KD et al have recently reported that AR was not associated with an increased risk of COVID-19-related hospitalization.⁷ Collectively, these results indicate that primary AR may not modify the risk for COVID-19.

In line with recent reports,^{8,9} we found that type 2 cytokines downregulated, whereas IFNs upregulated ACE2 gene expression in HNECs. However, ACE2 expression correlated with IFN response, but not type 2 response, in nasal tissues and epithelial cells, underscoring a predominant role of IFNs in regulating ACE2 expression in upper airways.⁹

Allergic rhinitis and allergic asthma are frequently co-occurred and may share common immune-pathogenic mechanisms such as type 2 inflammation. However, we found that patients with concomitant AR and allergic asthma had reduced ACE2 expression in bronchial epithelial cells, which is likely regulated by type 2 response. The difference in ACE2 expression in allergic nasal and bronchial epithelial cells is possibly related to the different tension of IFN and type 2 response in upper and lower airways under allergic condition. Therefore, the counter effect of IFN and type 2 response may have an important role in regulating ACE2 expression in airways. The reduced ACE2 expression in allergic asthmatics may suggest a lower risk for COVID-19. Low prevalence of asthma (0%–0.9%) was observed in patients with COVID-19 in several studies in China.⁴ In a USA cohort, Chhiba et al⁷ recorded a relatively high prevalence of asthma (14%); however, there was no significant difference in hospitalization rate or mortality between patients with and without asthma.

Our study has several limitations. First, self-reported symptoms and comorbidities might lead to the potential misestimation of the prevalence and the strength of association with the clinical outcomes. Second, we did not include fatal cases since no subsequent follow-up confirmation of comorbidities could be made for them. Third, we could not get the demographic information of subjects in the public gene dataset, and the number of subjects was limited. We therefore could not preclude the potential bias. However, the nasal epithelial cell results were consistent with our nasal tissue results derived from a relatively larger cohort.

In conclusion, for the first time, we provide the evidence that AR comorbidity may not have significant modifying effect on the development and expression of COVID-19. ACE2 expression is not altered in AR patients. ACE2 gene expression in airways is regulated, at least in part, by the counter effect of type 2 and IFN inflammation.

KEYWORDS

allergic rhinitis, angiotensin-converting enzyme II, coronavirus disease 2019, cytokine, epithelial cell

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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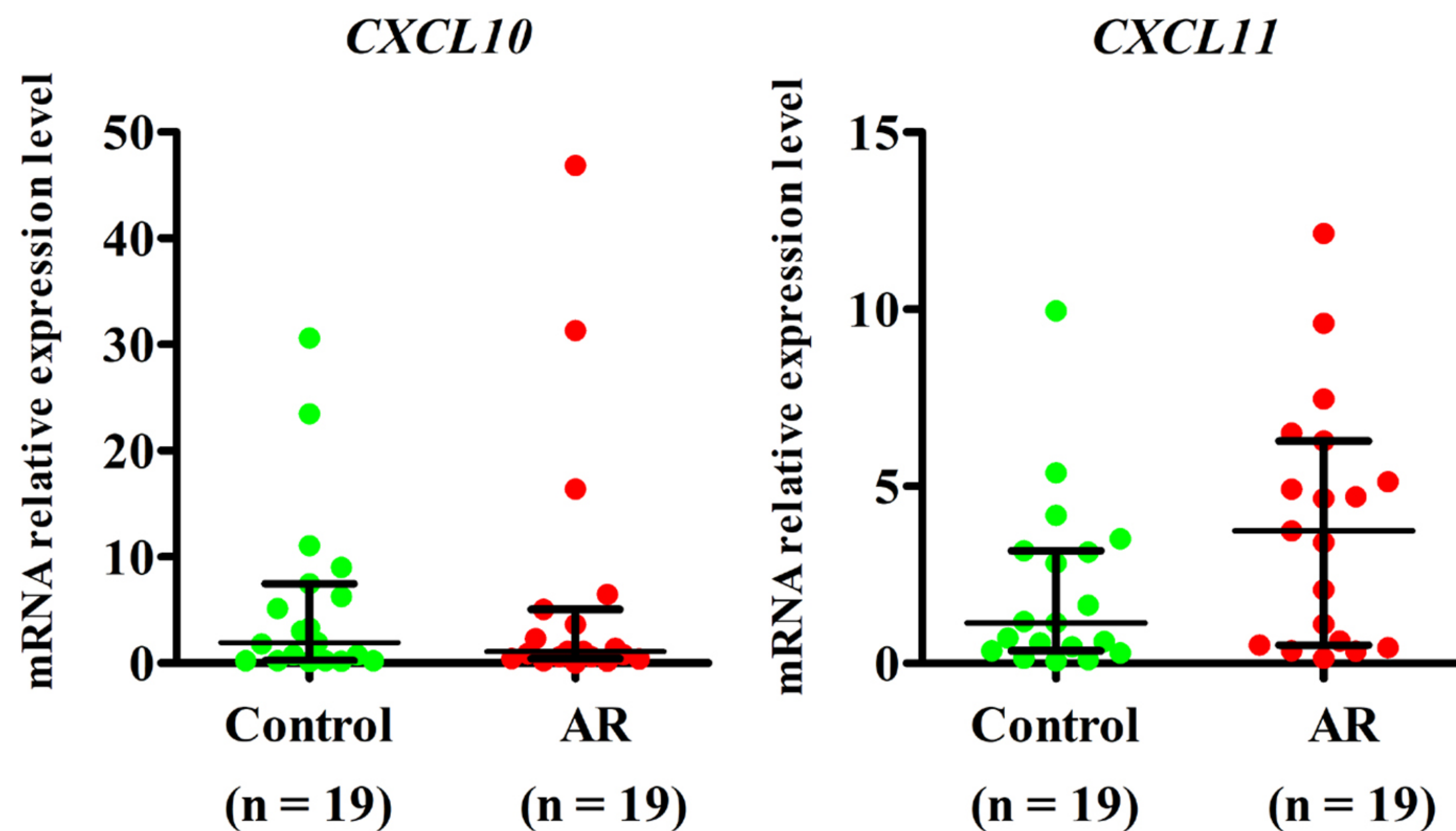
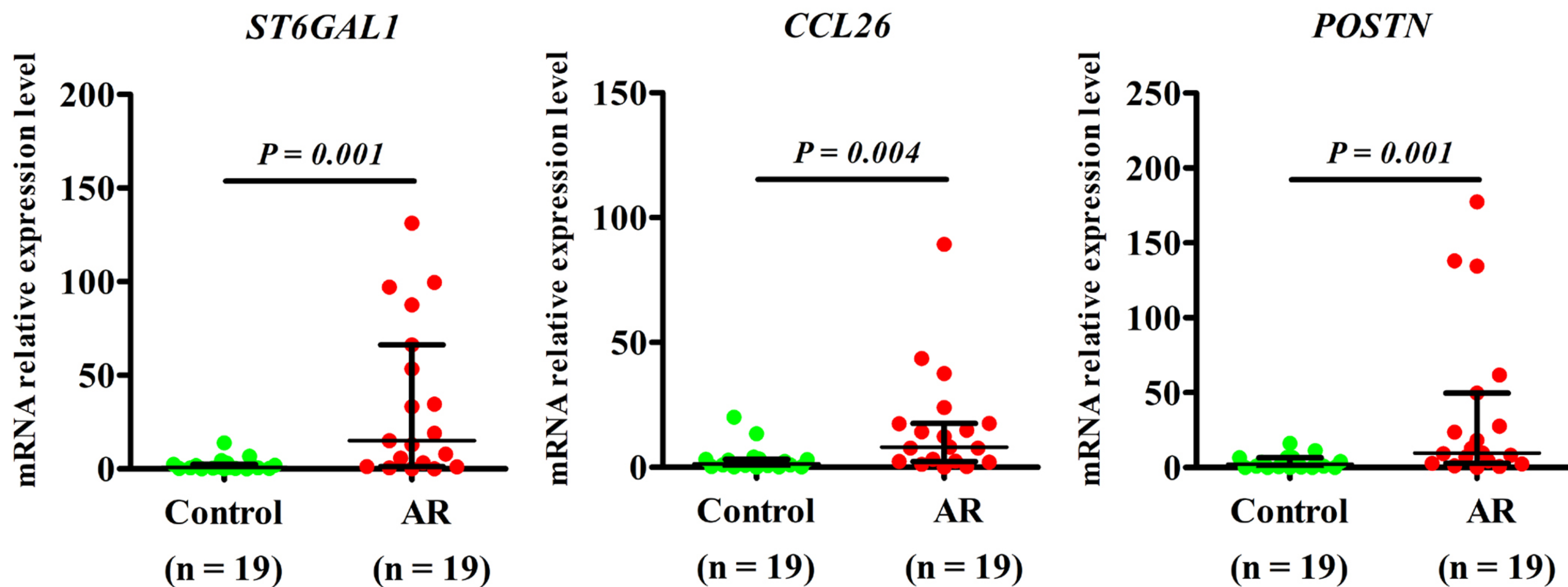
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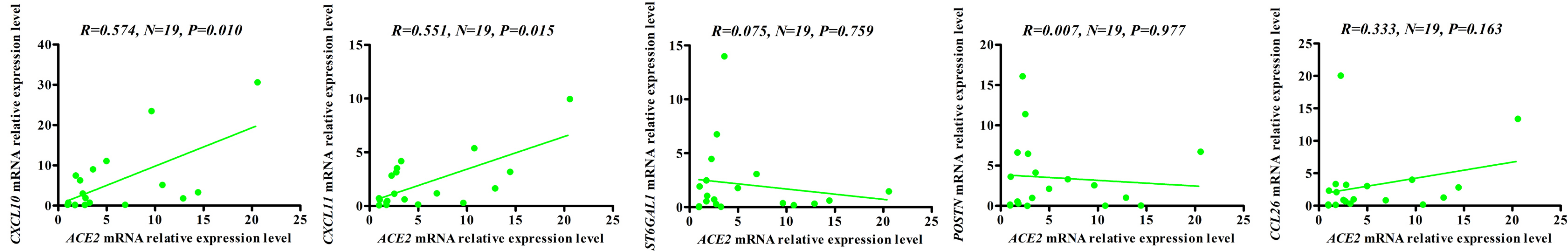
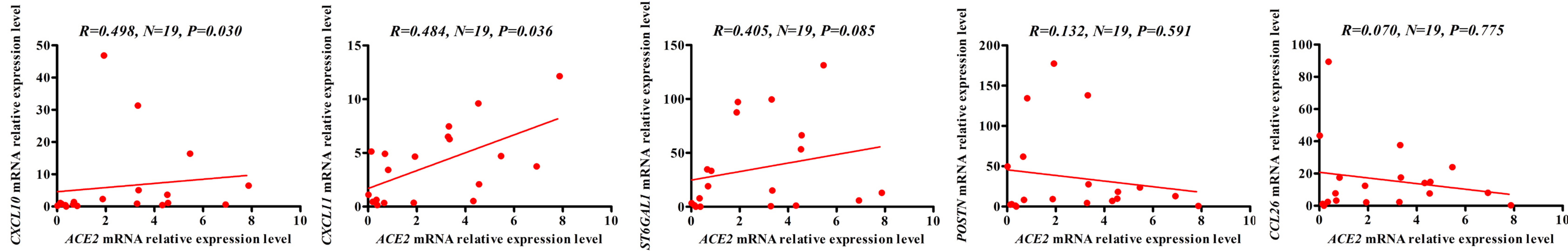
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SUPPORTING INFORMATION

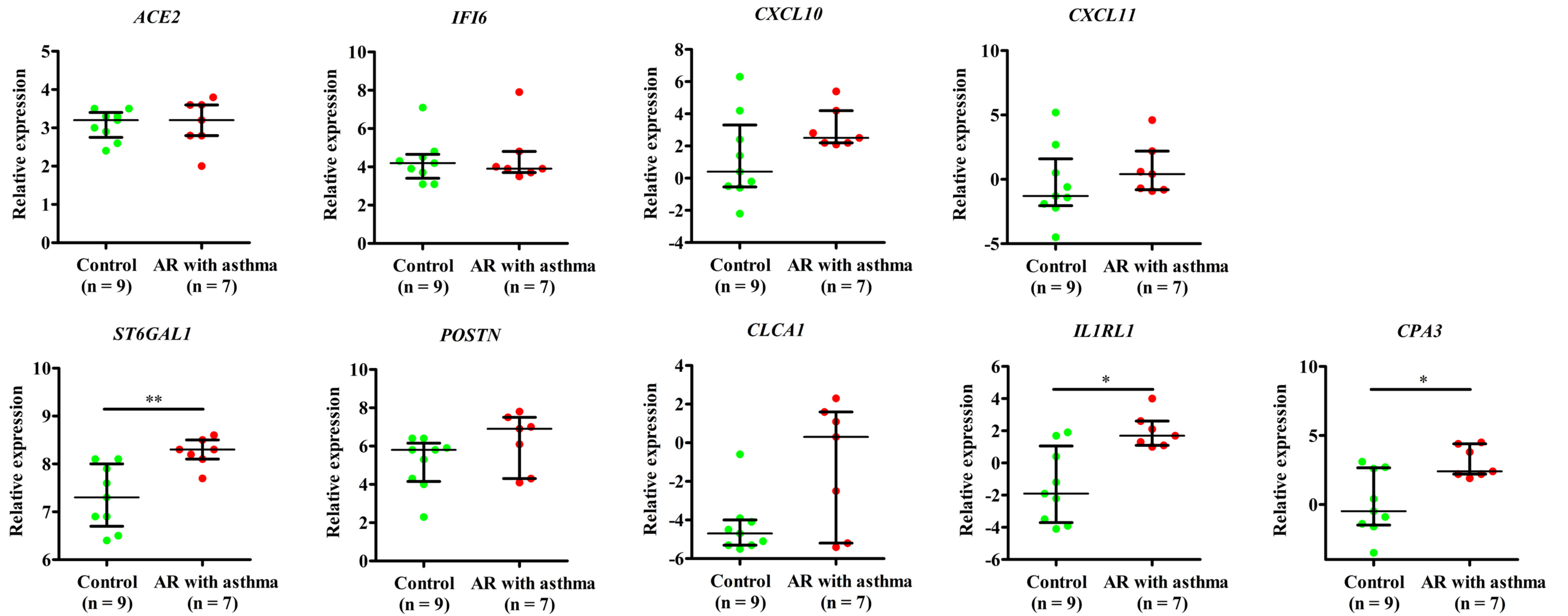
Additional supporting information may be found online in the Supporting Information section.

A**B**

A**Control tissue****B****AR tissue**

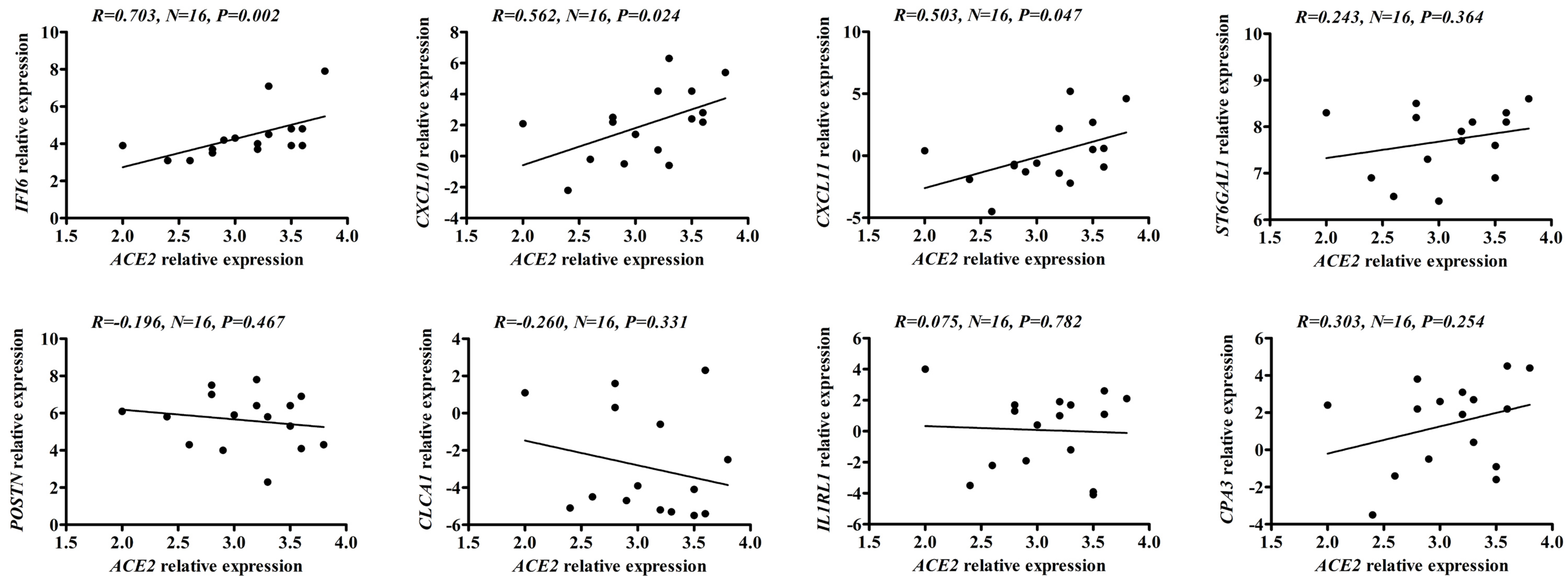
A

Nasal brushings

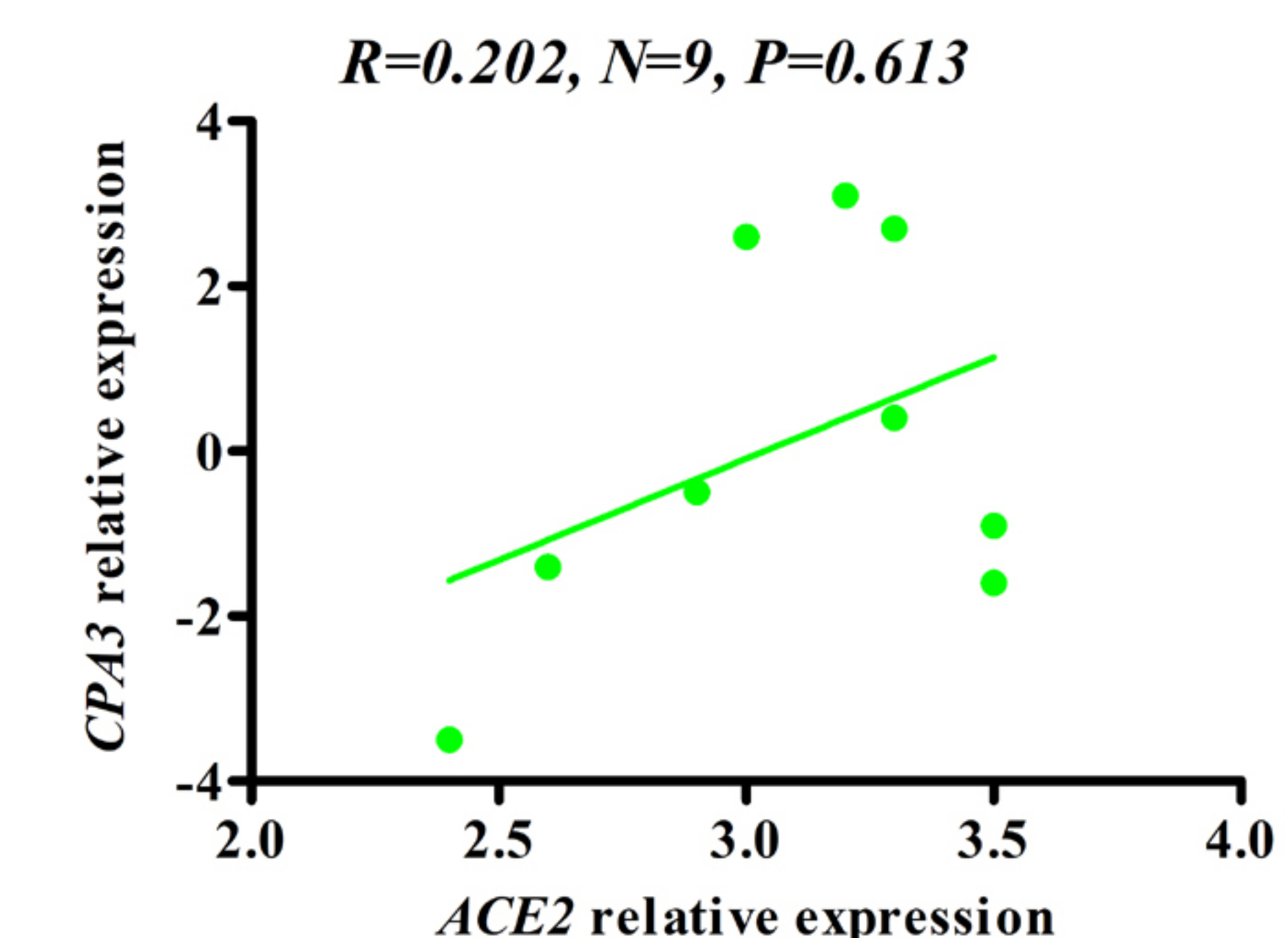
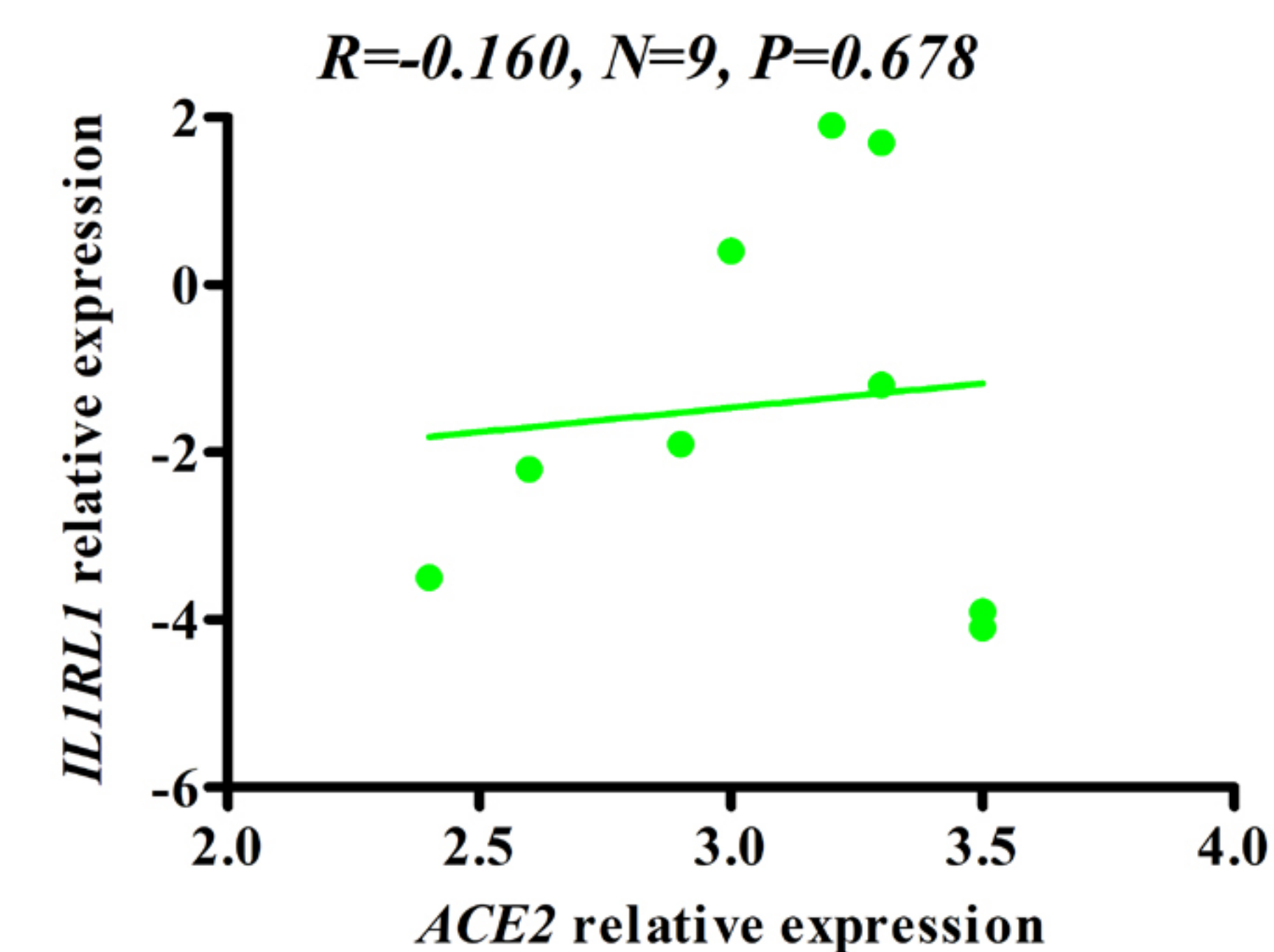
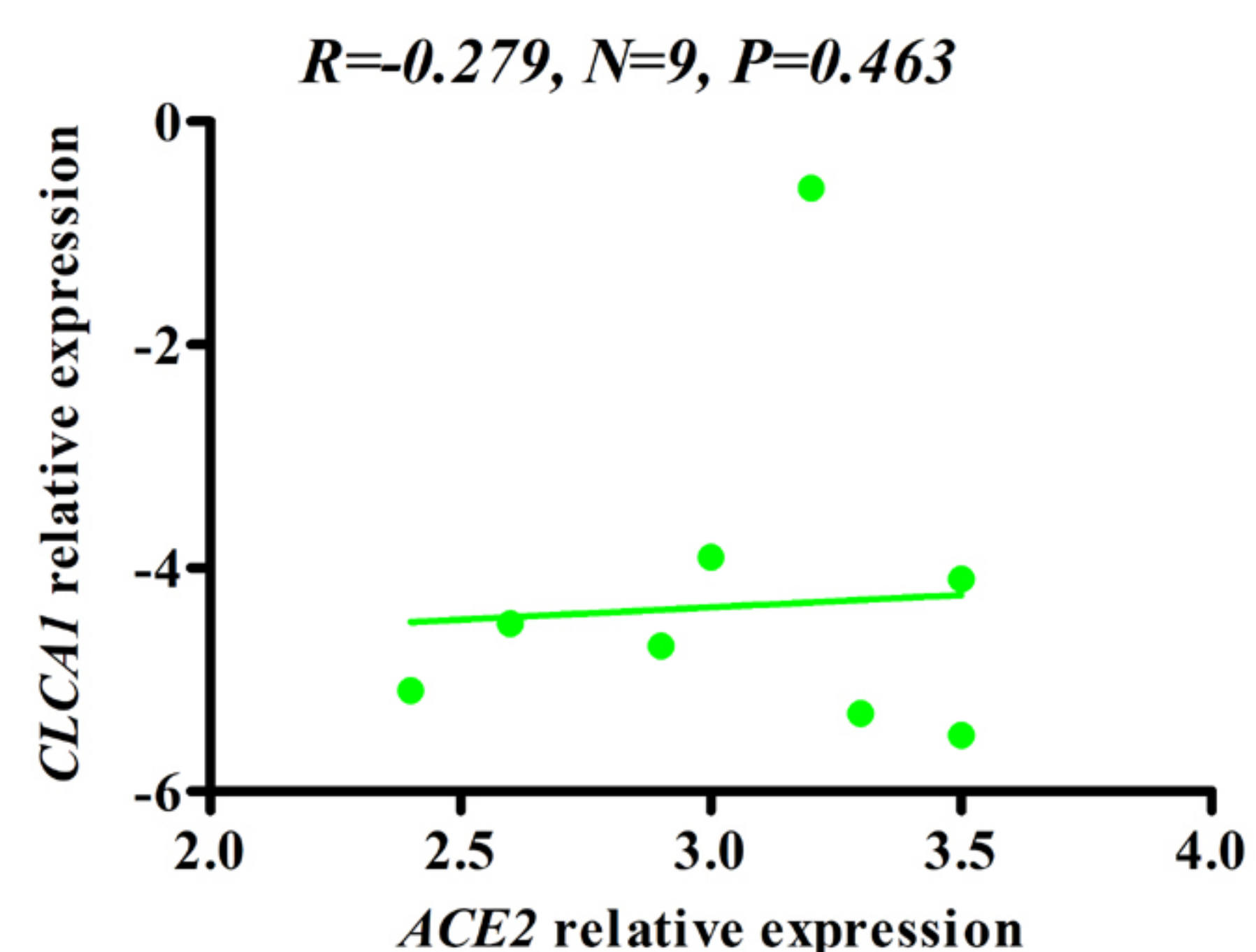
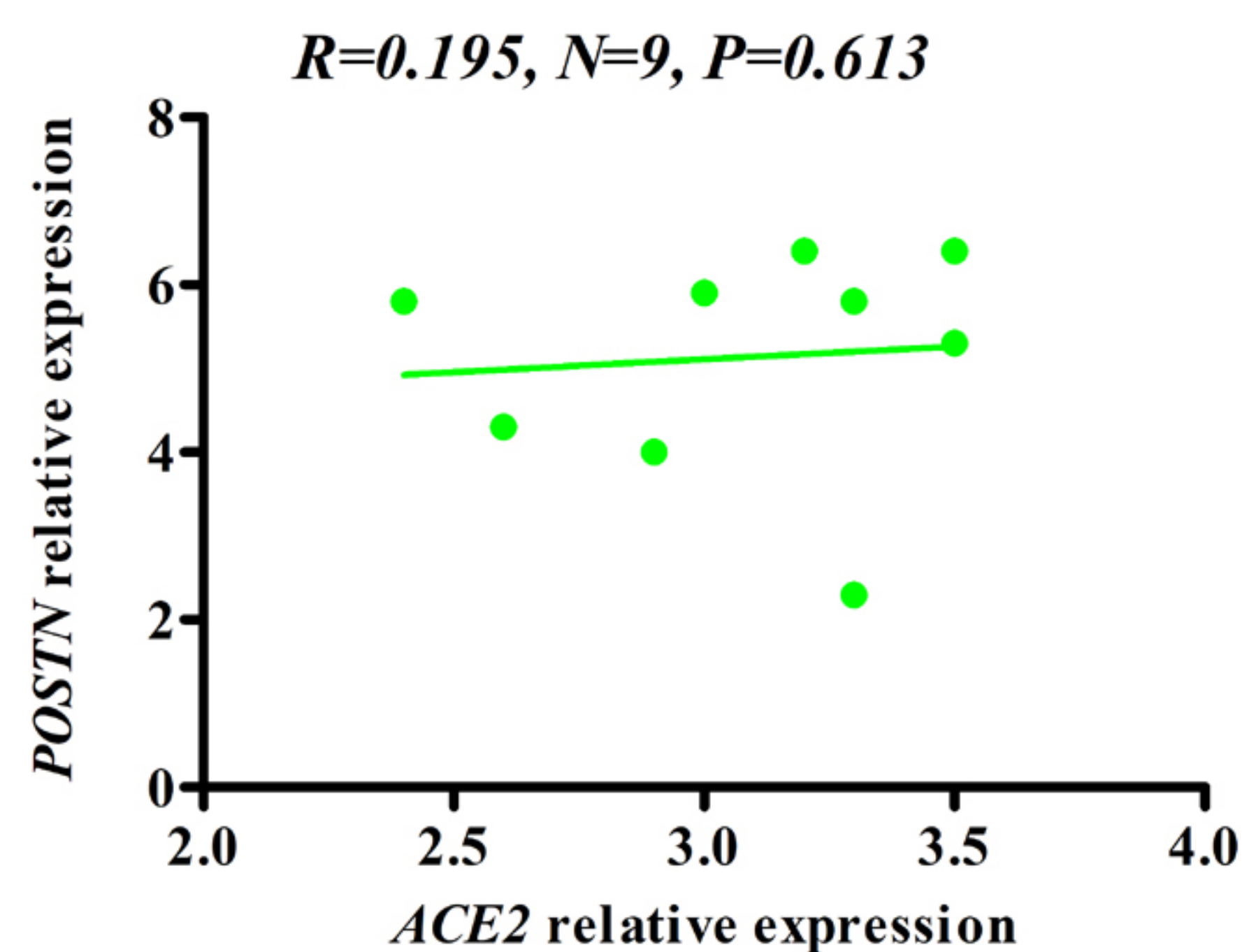
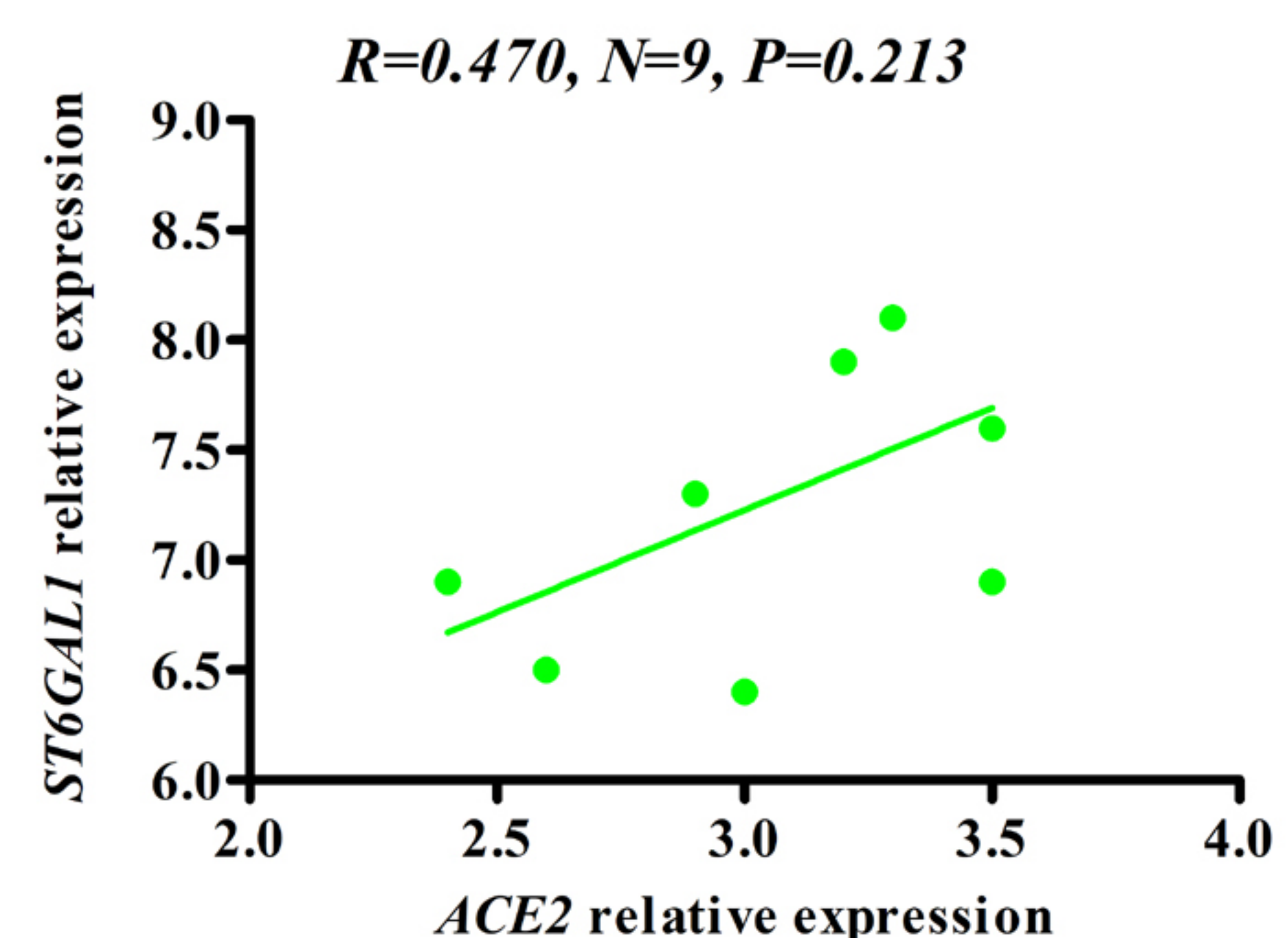
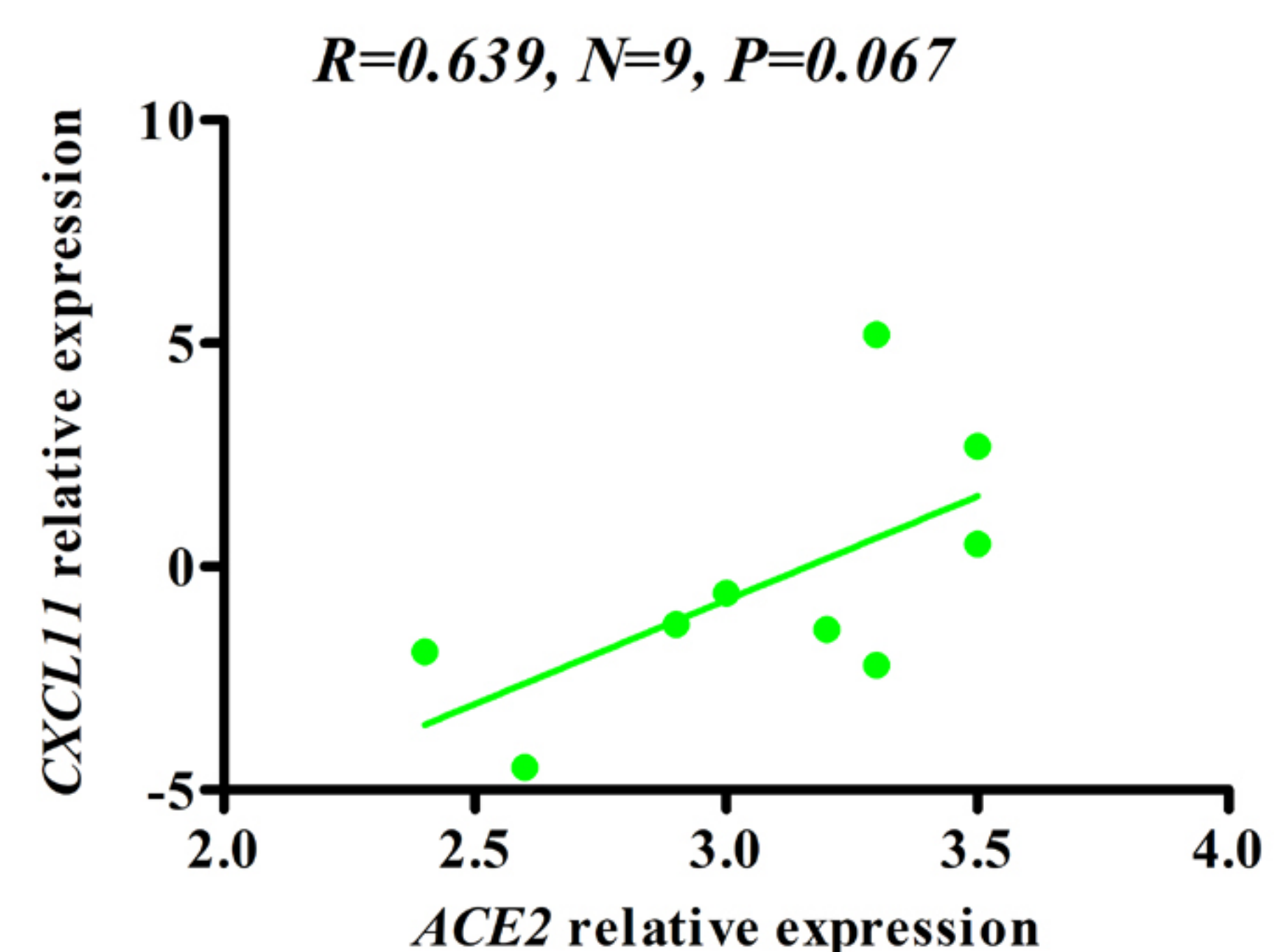
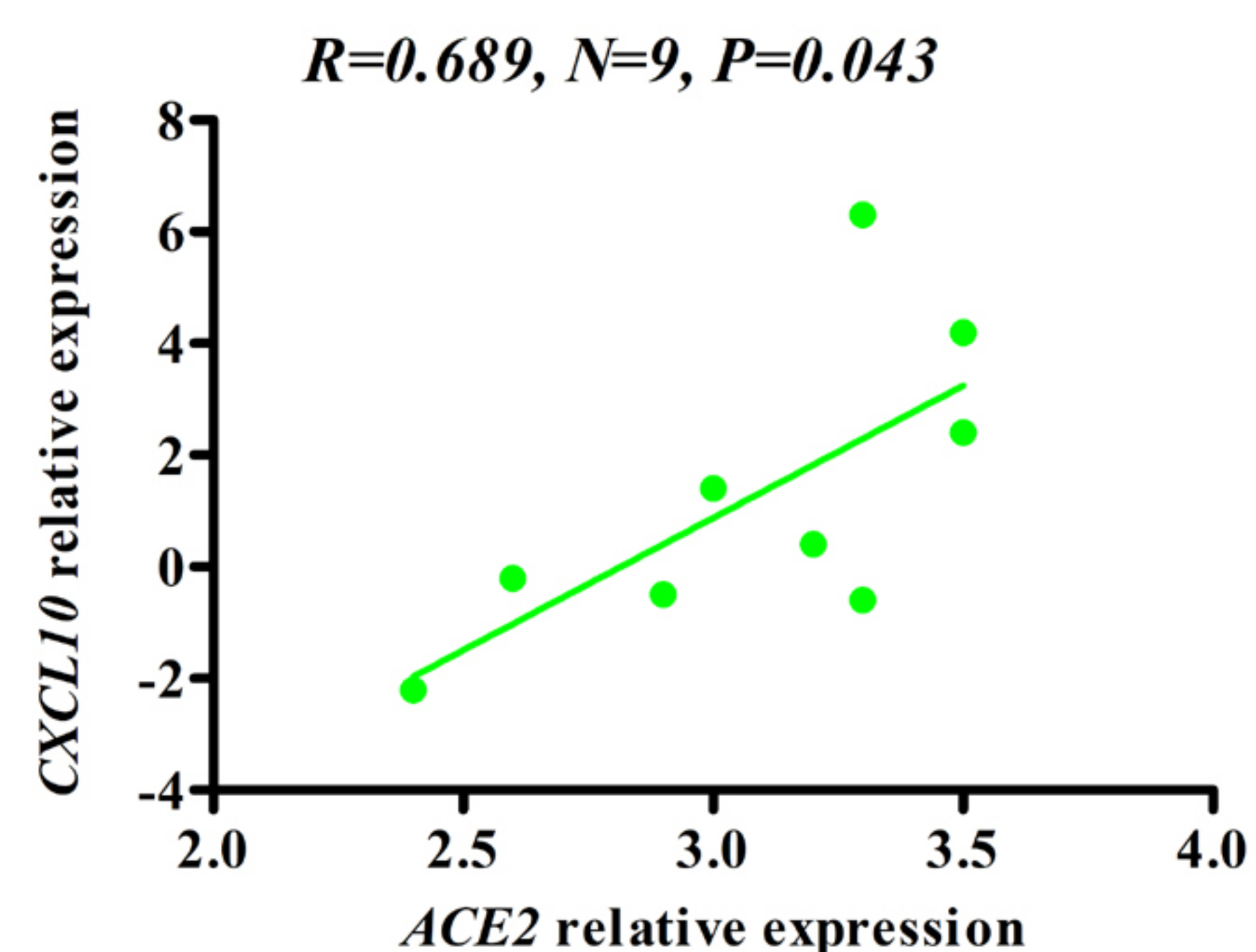
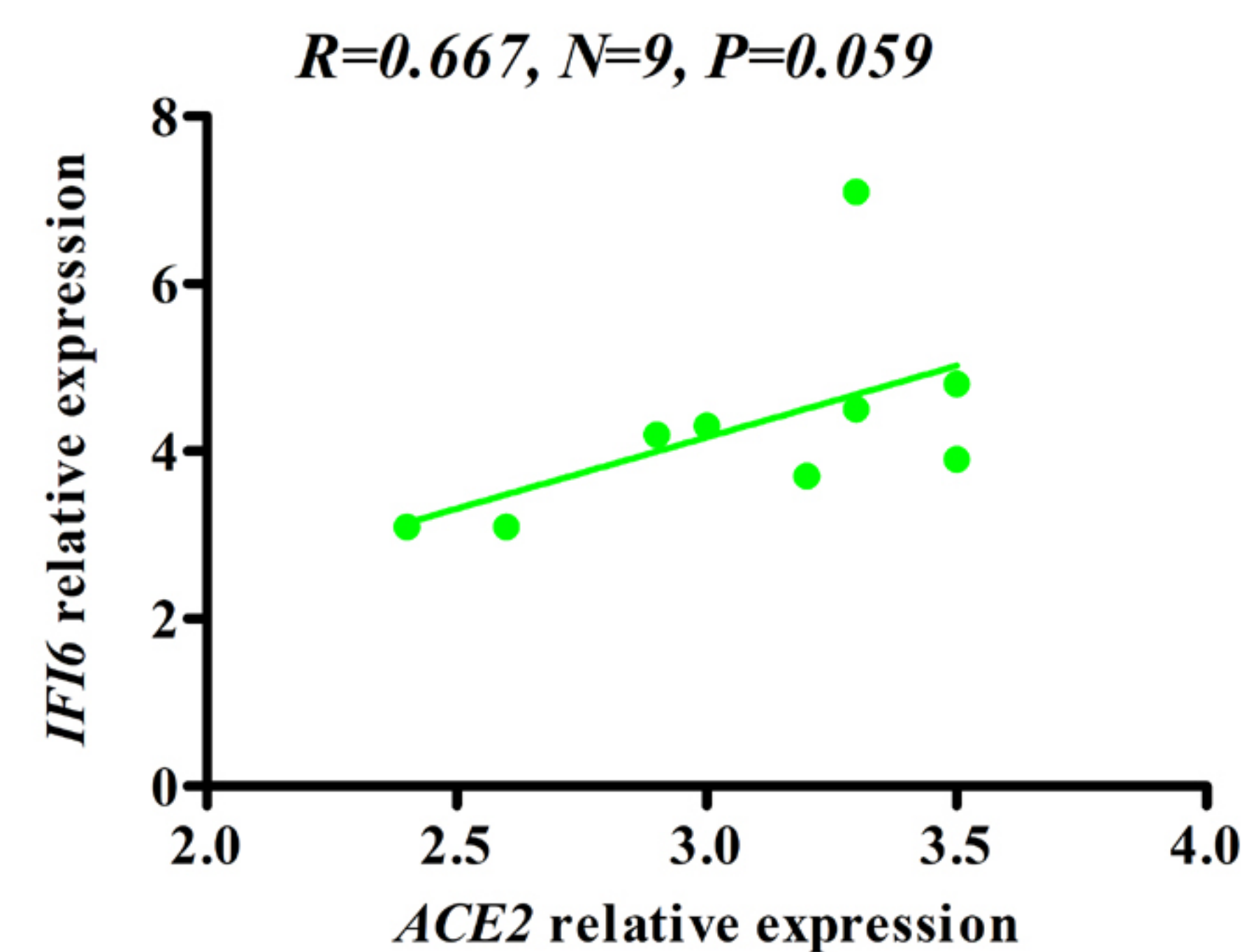


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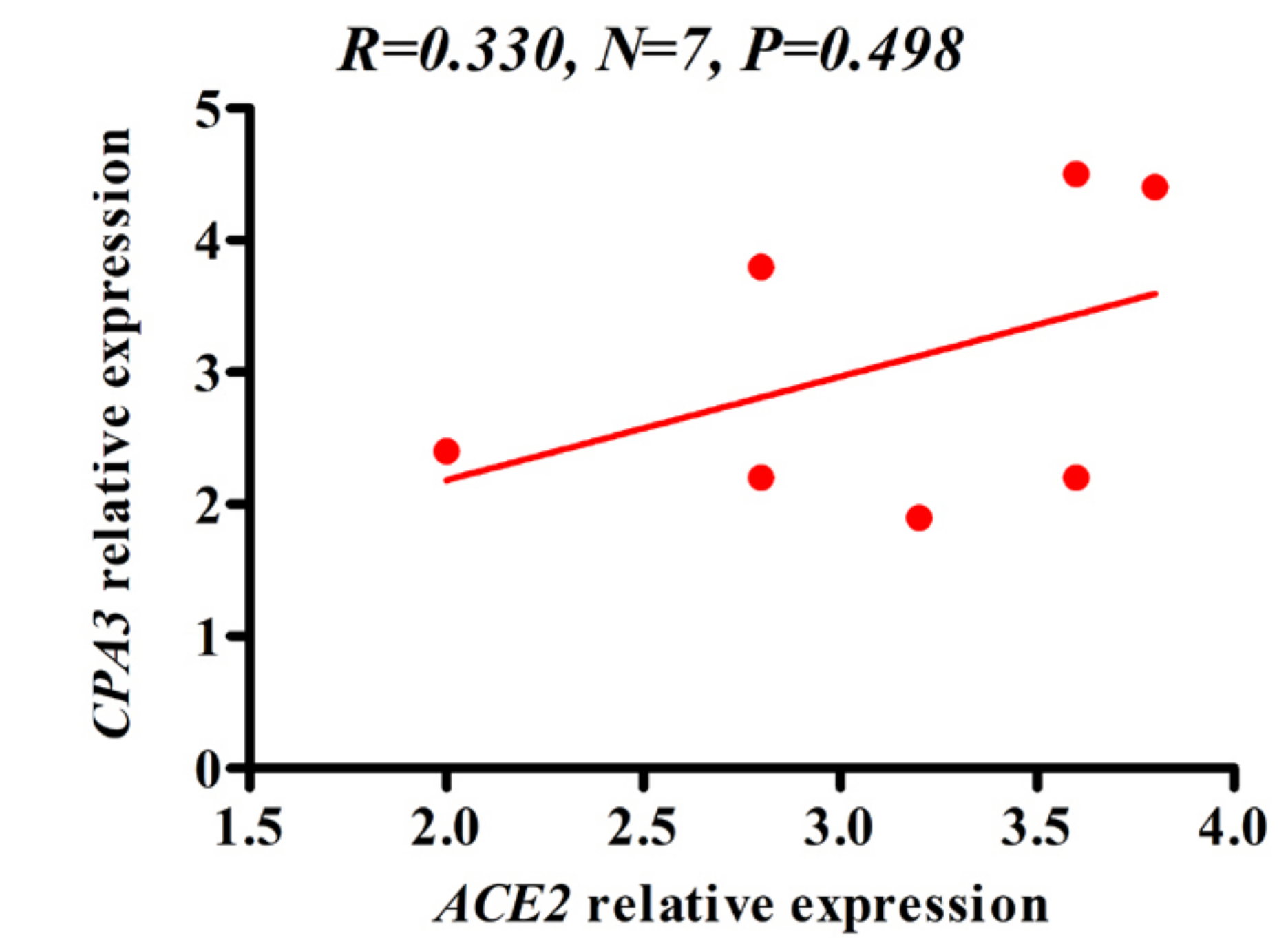
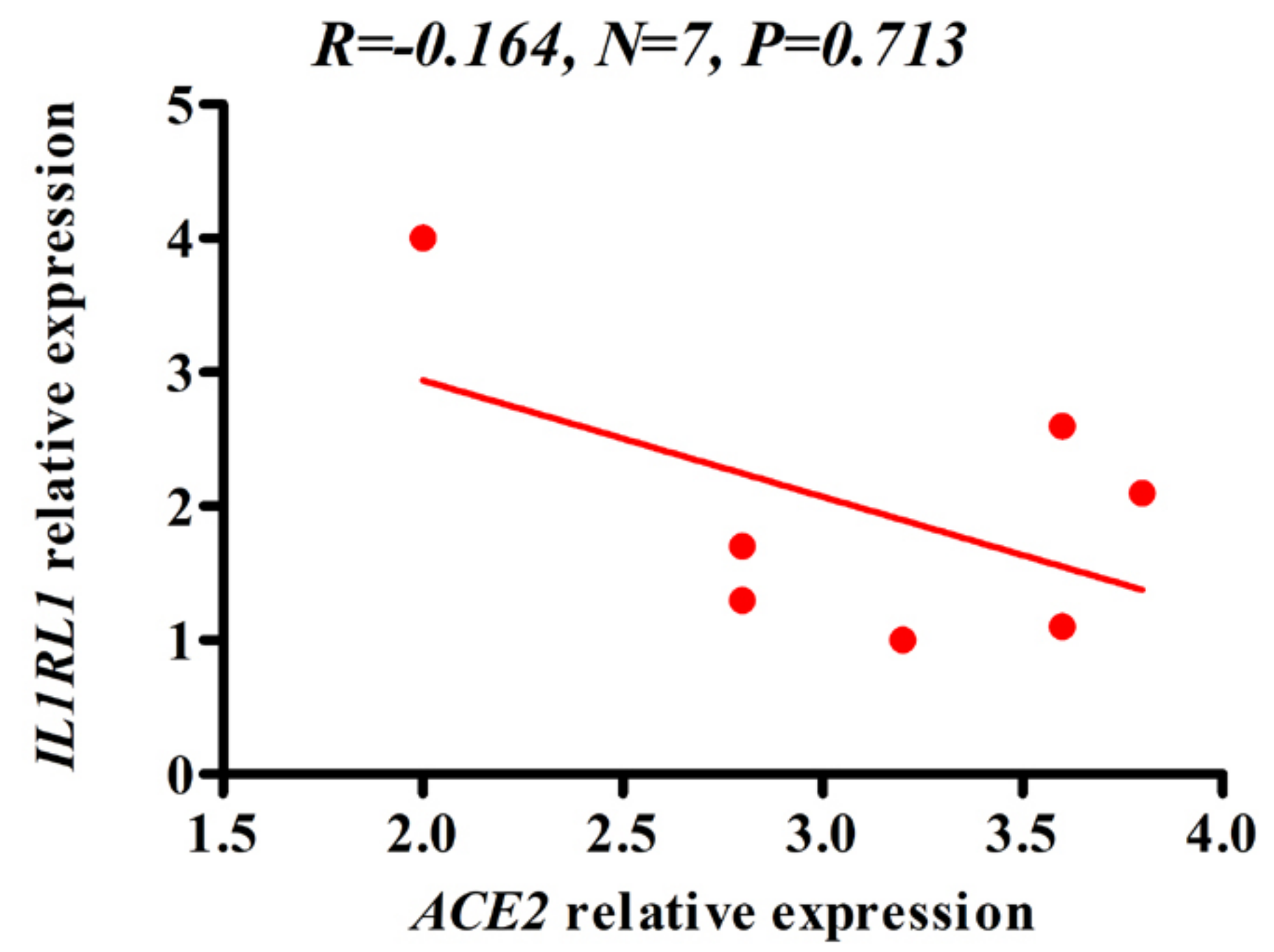
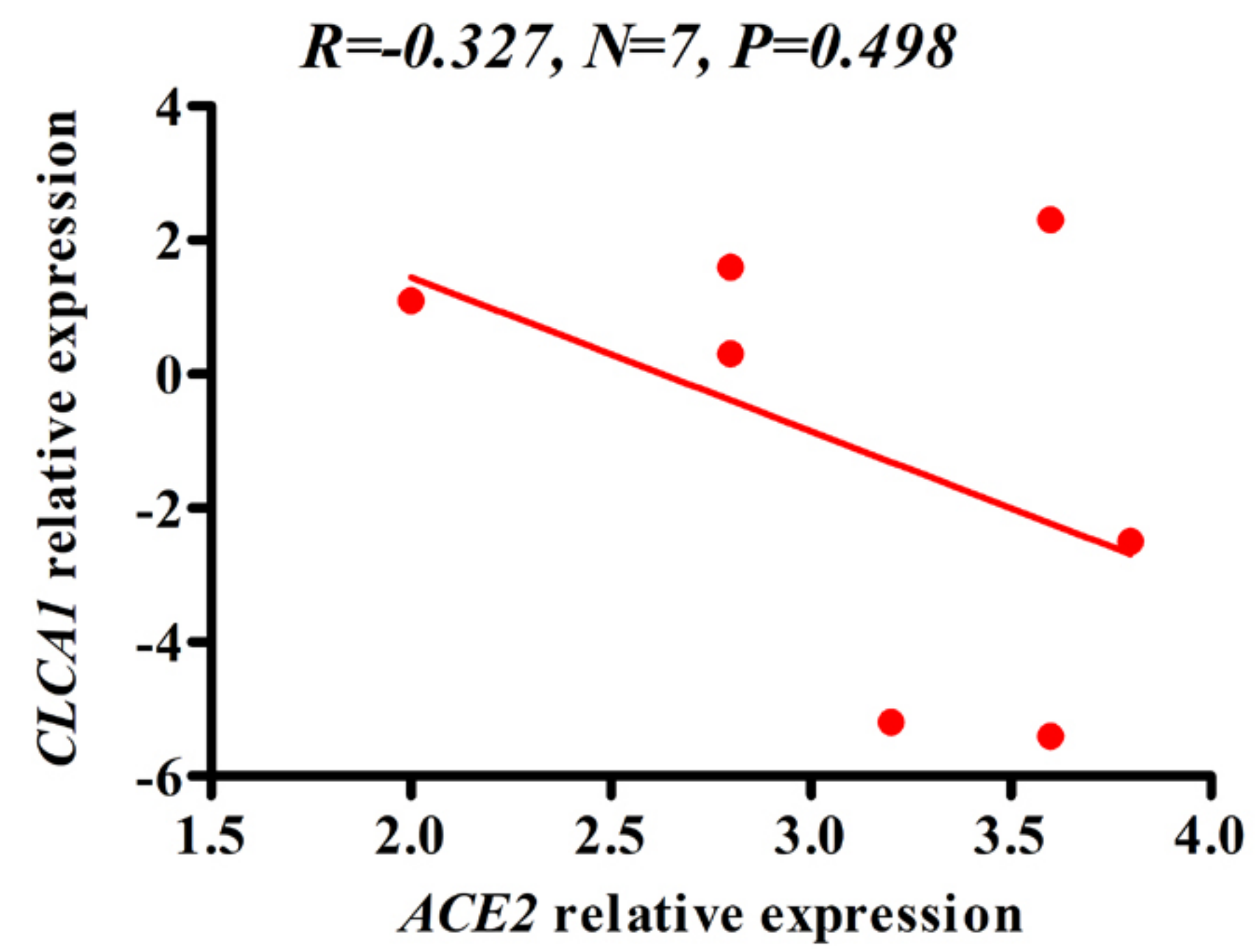
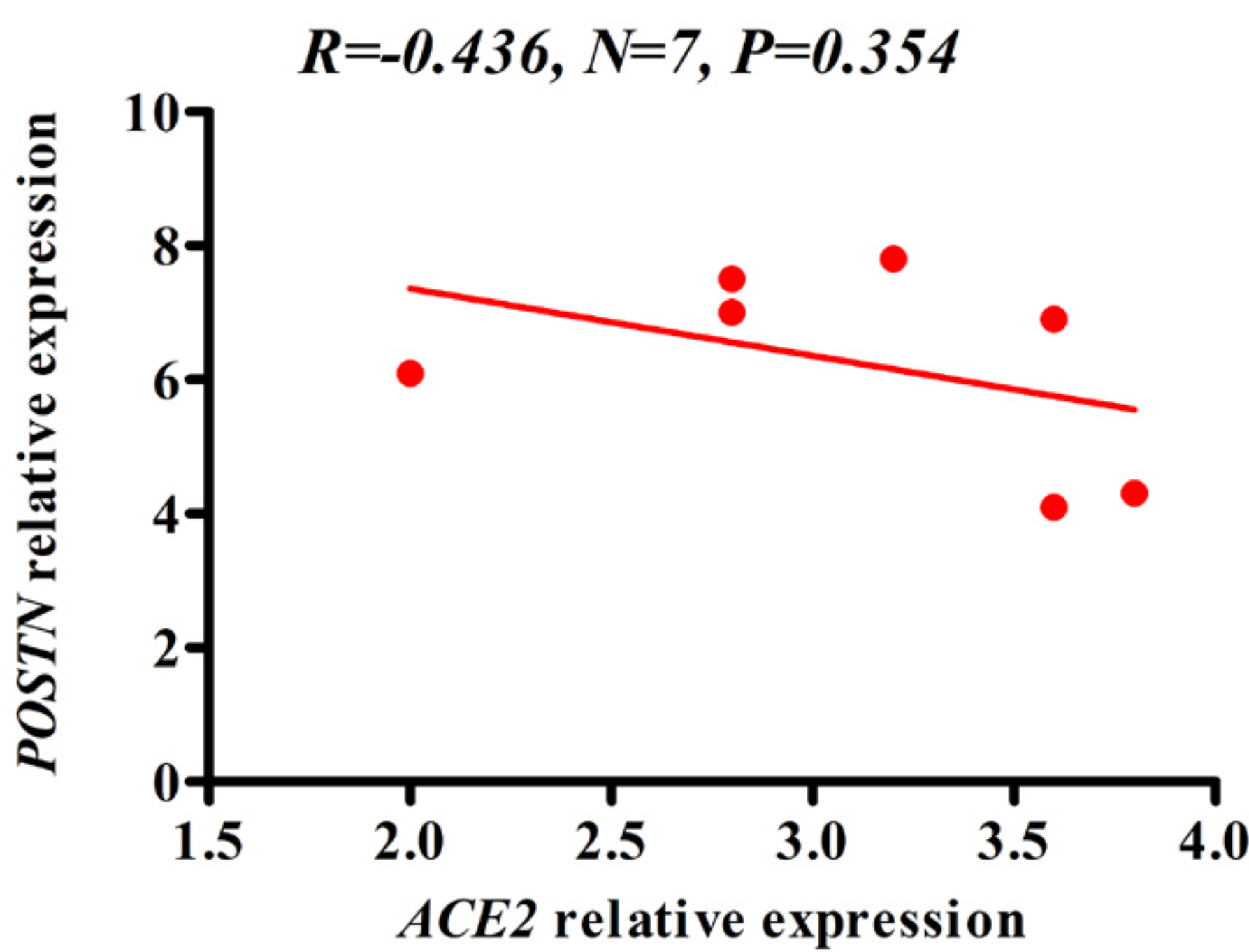
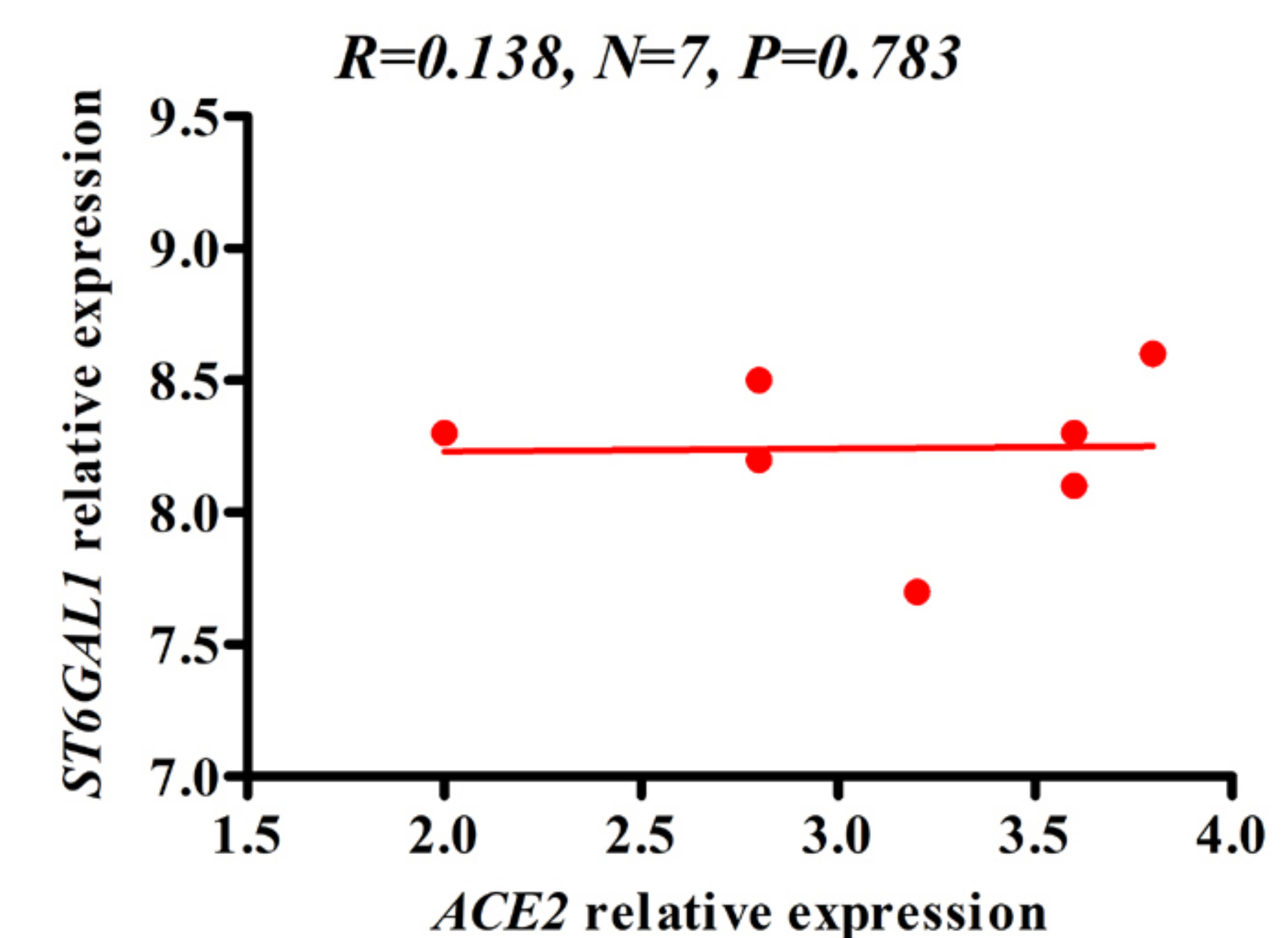
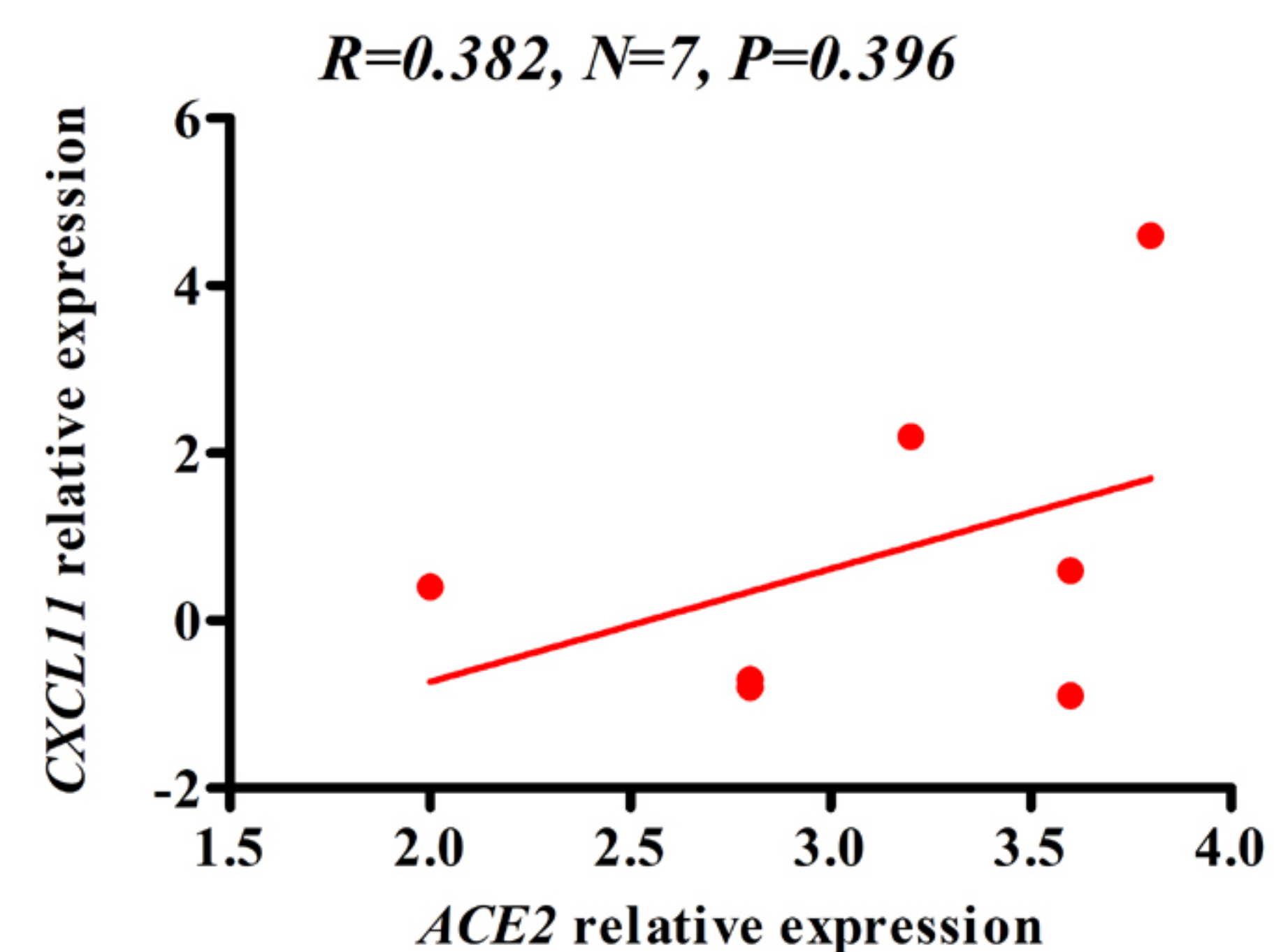
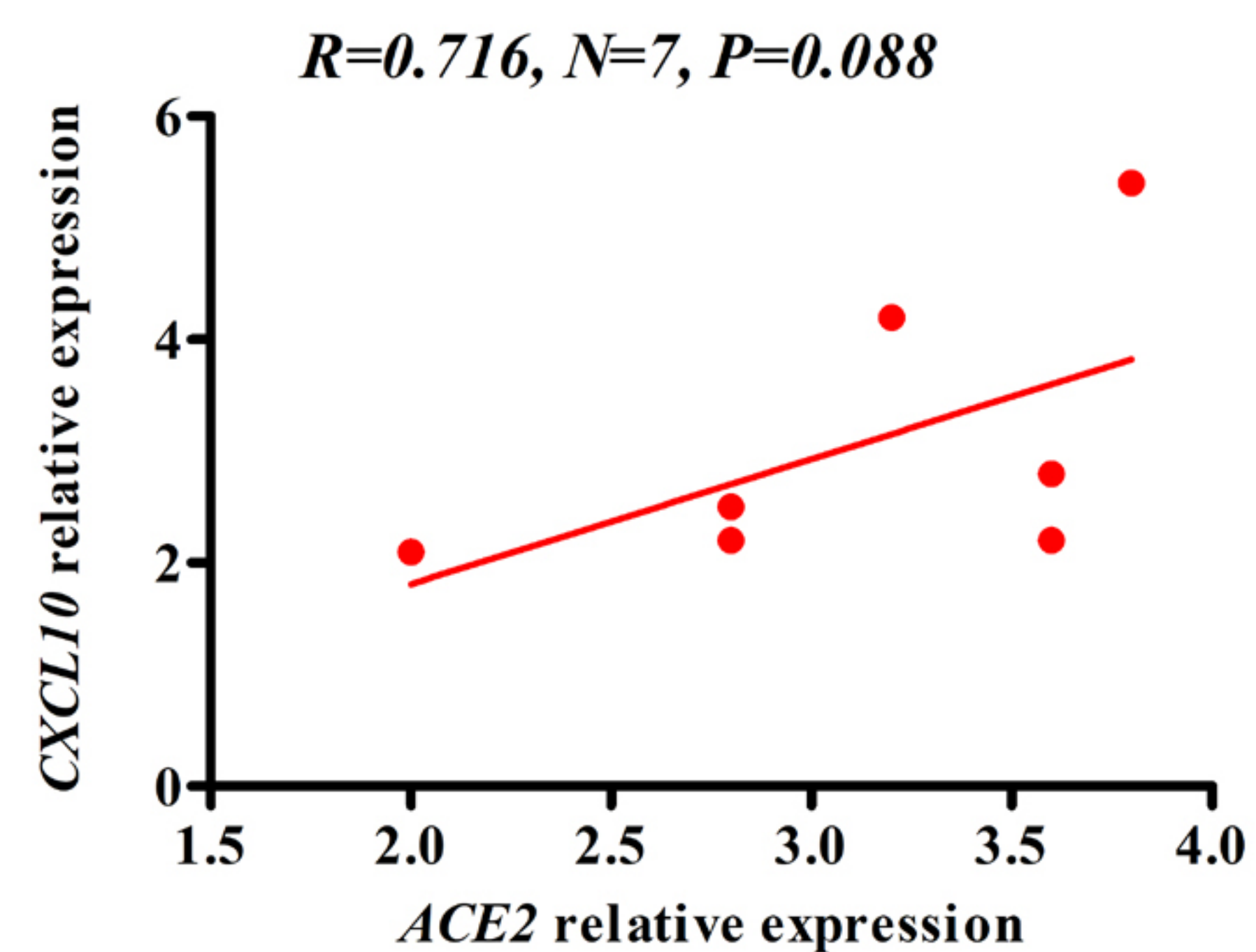
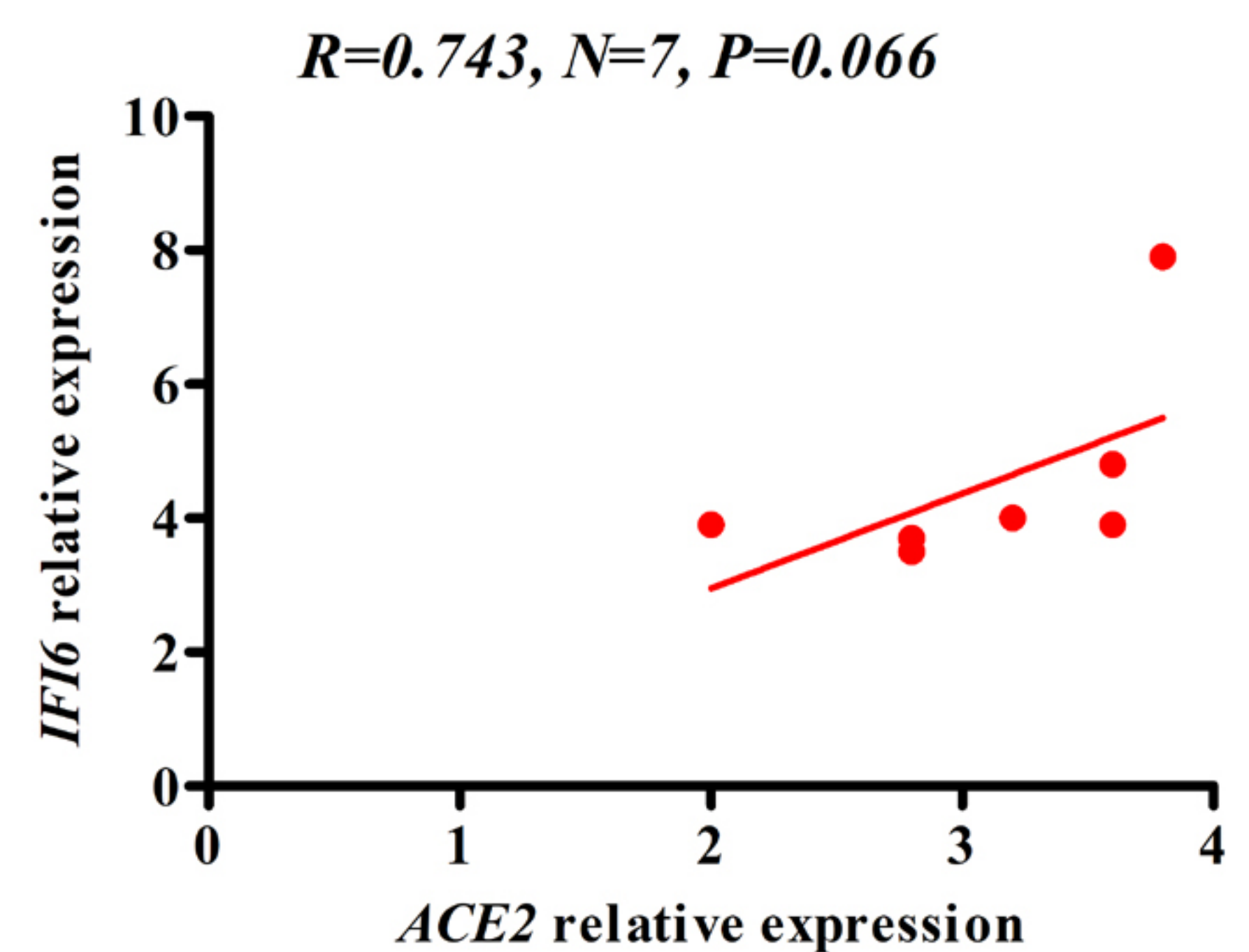
Nasal brushings

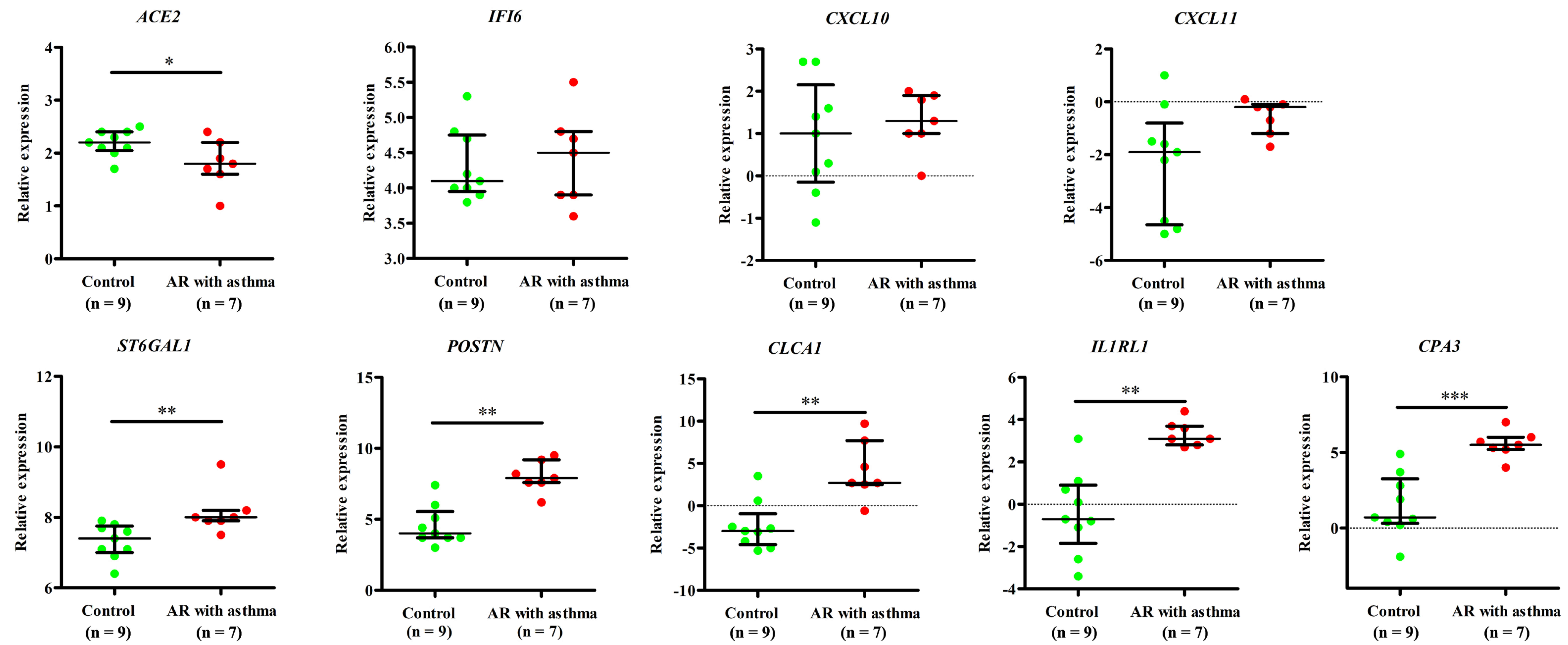
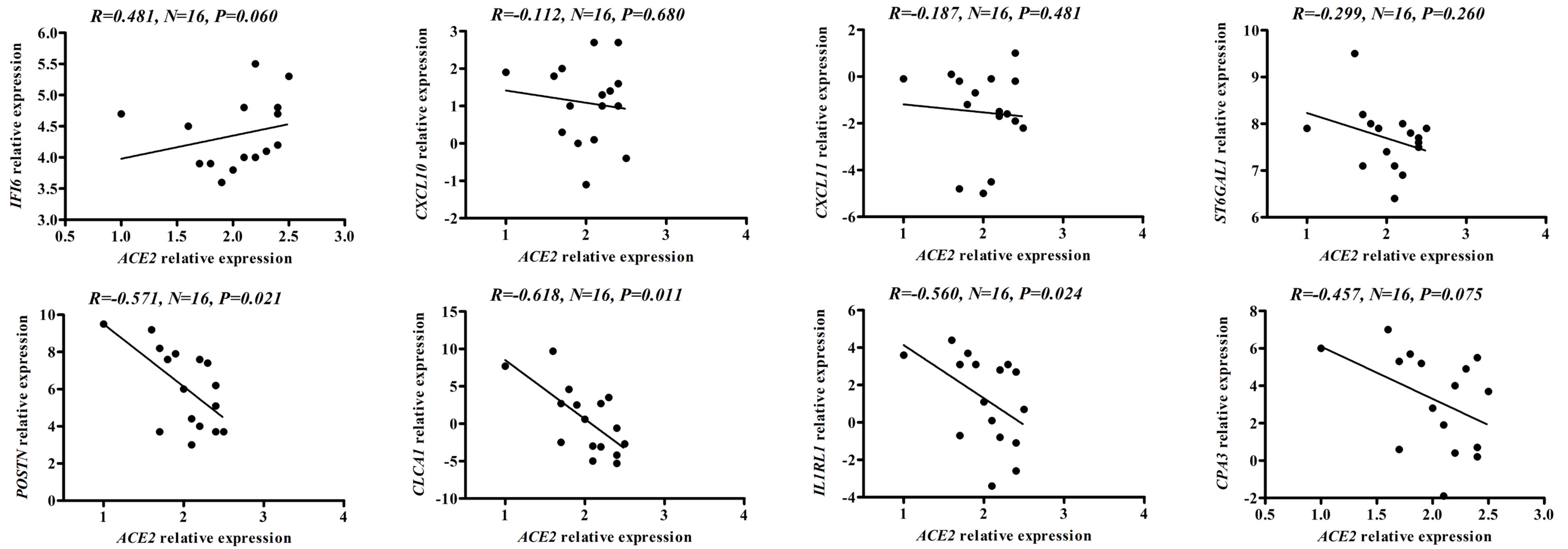


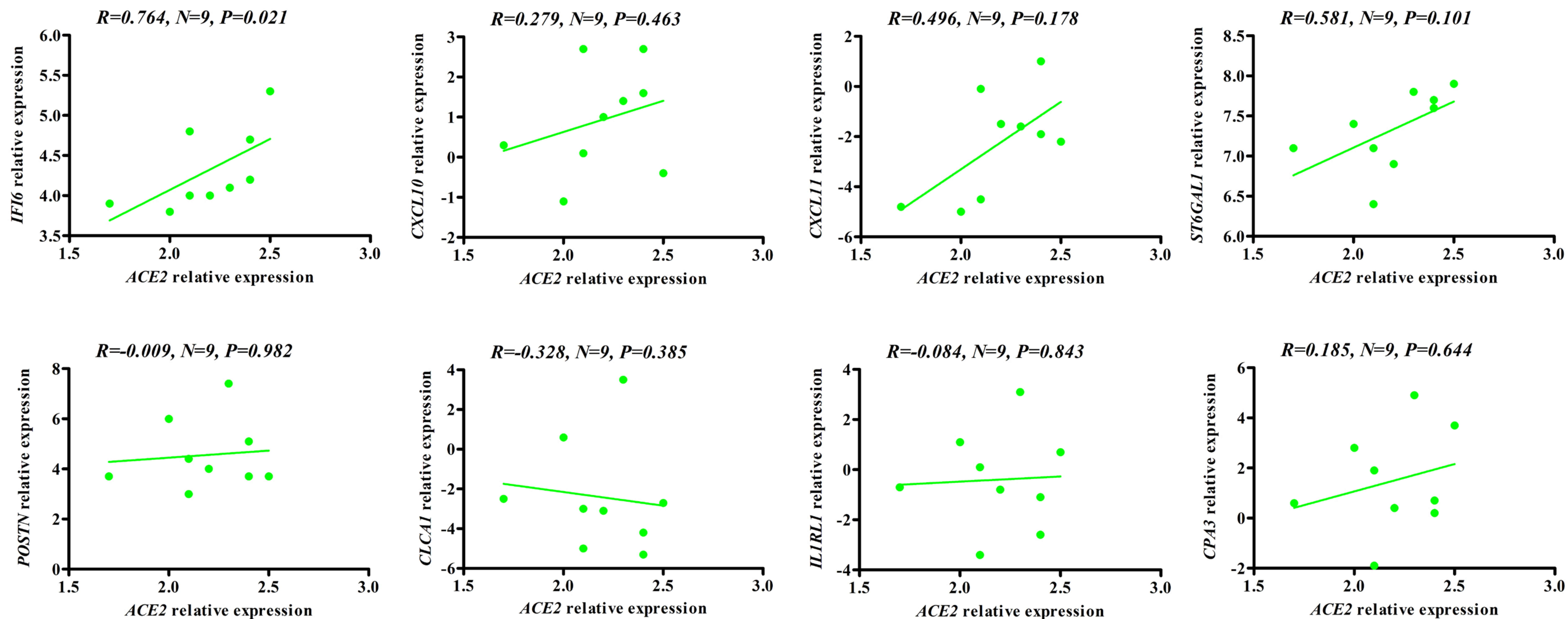
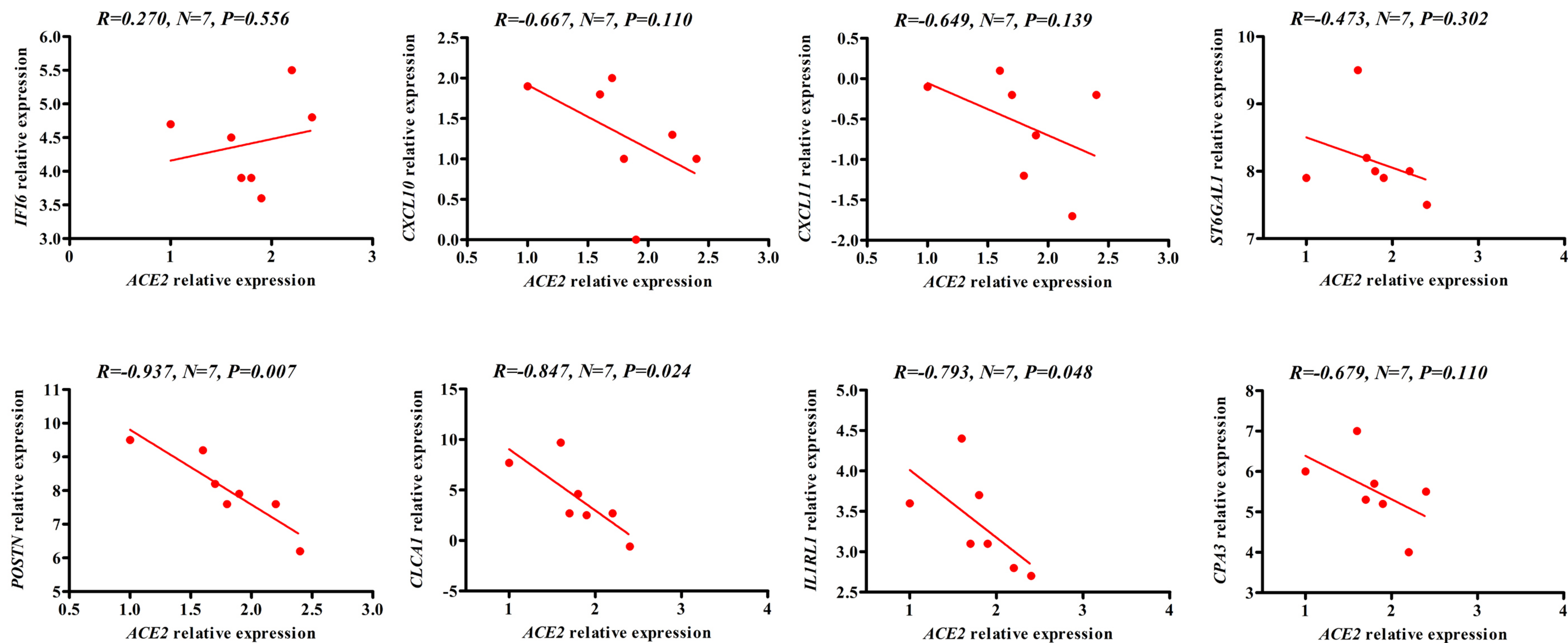
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Nasal brushings
from control

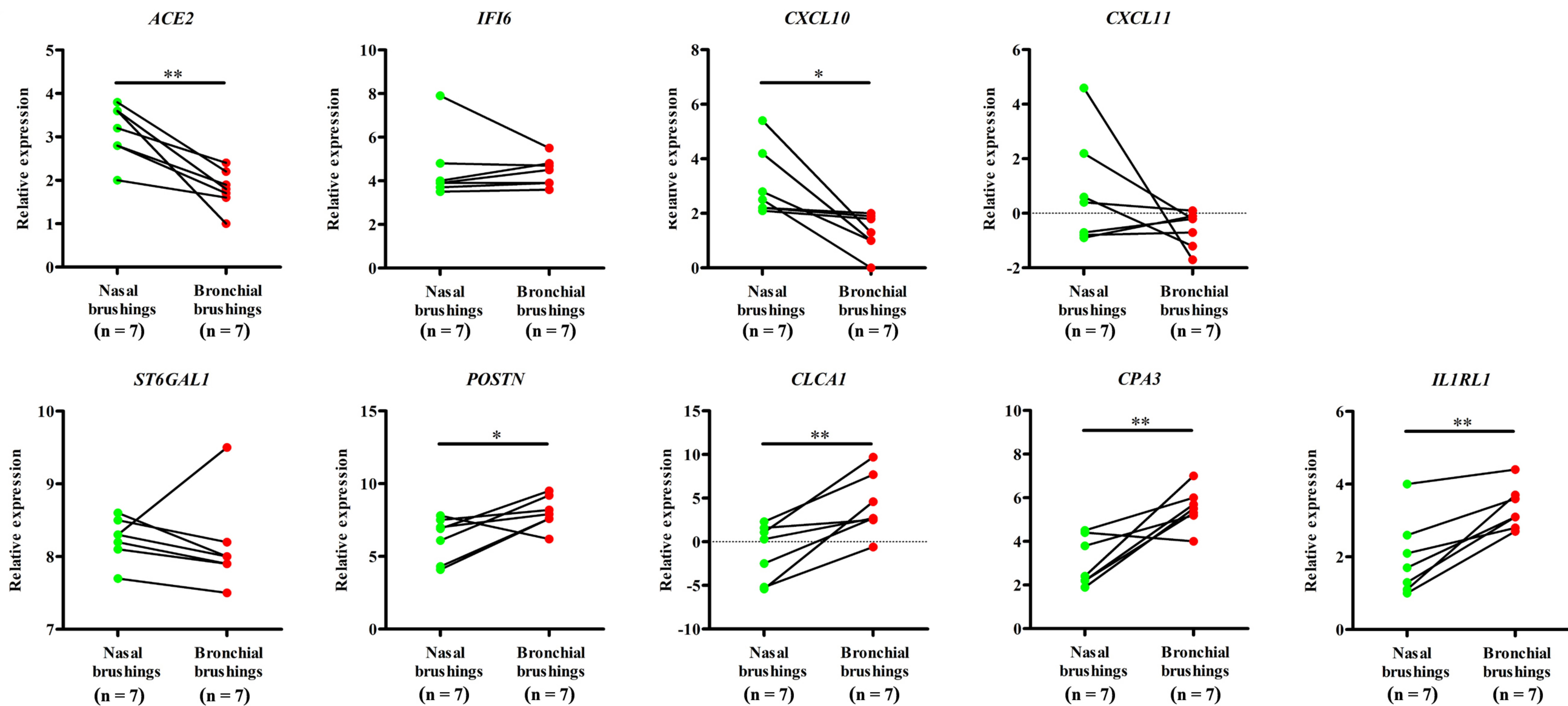
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Nasal brushings
from AR with asthma

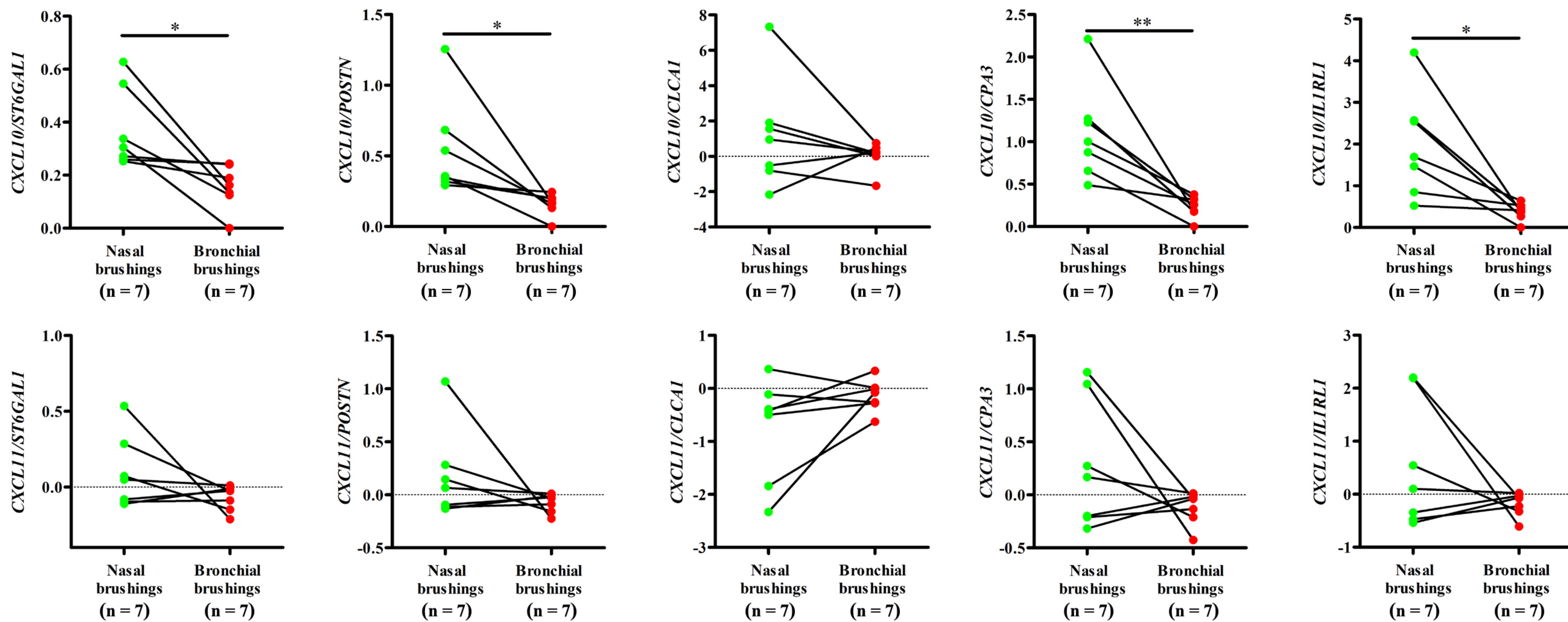
A**Bronchial brushings****B****Bronchial brushings**

A**Bronchial brushings
from control****B****Bronchial brushings
from AR with asthma**

A



B



Appendix S1

Online Repository

ACE2 expression and its implication in the association between COVID-19 and allergic rhinitis

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Running title: AR and COVID-19

Conflict of interest statement: None

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METHODS

Study design and participants

A total of 1,172 etiologically confirmed COVID-19 patients, who was discharged from Tongji Hospital, the largest designated hospital to treat patients with COVID-19 in Wuhan, China, between January 27, 2020 and March 10, 2020 and completed the telephone follow-up on the 30th (± 2) day after discharge, were retrospectively enrolled for the study of characteristics of COVID-19. The diagnosis of COVID-19 was based on the guidance for diagnosis and management of COVID-19 released by World Health Organization.^{S1} The diagnosis was based on the positive result of the real-time reverse-transcriptase-polymerase-chain-reaction assay for SARS-CoV-2 of throat or nasopharyngeal swab specimens. Patients with COVID-19 were classified into severe or non-severe type on admission according to the American Thoracic Society guidelines for community-acquired pneumonia.^{S2} Patients who met one major criterion or three or more minor criteria were defined as severe type: major criteria: 1. Septic shock with need for vasopressors; 2. Respiratory failure requiring mechanical ventilation; minor criteria: 1. Respiratory rate ≥ 30 breaths/min; 2. PaO₂/FiO₂ ratio ≤ 250 ; 3. Multilobar infiltrates; 4. Confusion/disorientation; 5. Uremia (blood urea nitrogen level ≥ 20 mg/dL); 6. Leukopenia (white blood cell count $< 4,000$ cells/ μ L); 7. Thrombocytopenia (platelet count $< 100,000$ / μ L); 8. Hypothermia (core temperature $< 36^{\circ}\text{C}$); 9. Hypotension requiring aggressive fluid resuscitation. Comorbidities were determined based on patient's self-report on admission and reevaluated by experienced physicians

during follow-up. This study focused on AR comorbidity in COVID-19 patients.

In addition, a total of 58 patients undergoing nasal septoplasty, including 29 with and 29 without AR, were enrolled for the immunohistochemistry, RT-PCR and cell culture study. Patients' characteristics were provided in the Table S1. Atopic status was evaluated by using skin prick test with a panel of common inhalant allergens and/or by using the ImmunoCAP to detect IgE antibodies against common inhalant allergens (Phadia, Uppsala, Sweden) in our region.^{S3} The diagnosis of AR was based on the concordance between the atopic status and typical allergic symptoms. All AR patients had positive skin prick test or specific IgE test to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farina*, and 14 patients also had positive test to other allergens including cockroach (20.7%), dog (17.2%) and cat (17.2%) dander, *Alternaria* (17.2%), and *Polulus* (10.3%) and *Platanus* (10.3%) pollen. Inferior turbinate mucosal samples were collected and human nasal epithelial cells (HNECs) were scraped from inferior turbinate during nasal septoplasty. Subjects were excluded if they had received any oral steroid within 3 months before the surgery, or under allergen immunotherapy. Topical steroids and antihistamines were withheld for a minimum of 1 month before the study. Not all samples were included in every experiment protocol because of limited quantity. This study was approved by the Ethics Committee of Tongji Hospital.

Clinical characteristic and laboratory assessment

COVID-19 patients' information of demographic characteristics, laboratory findings, treatments, and complications were obtained with data collection forms

extracted from electronic medical records. Laboratory measurements including routine blood, blood biochemistry, coagulation function, and infection biomarkers were performed. Patients' medical records were reviewed and analyzed by a well-trained team of physicians in Tongji Hospital. Acute liver injury was defined as jaundice with a total bilirubin level of ≥ 3 mg/dl and an acute increase in alanine aminotransferase of at least two times the upper limit of the normal range. Acute respiratory distress syndrome (ARDS) was defined as $\text{FiO}_2 \leq 300$ mmHg.^{S4,5} Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes Guideline with an abrupt decrease in kidney function and an increase in serum Cr to ≥ 1.5 times baseline.^{S6} Acute myocardial injury was defined as an elevated serum cardiac troponin (cTn) value above the 99th percentile upper reference limit.^{S7} Shock was defined as systolic arterial pressure < 80 mmHg and pulse pressure < 30 mmHg.^{S8}

***ACE2* gene expression analysis in patients with concomitant AR and asthma**

The RNA-seq data of nasal and bronchial brushings from 7 patients with concomitant AR and asthma and 9 healthy controls were acquired from the Gene Expression Omnibus (GEO) database under the series number GSE101720 and analyzed for the expression of *ACE2*, interferon (IFN) response genes [interferon alpha inducible protein (*IFI*) 6, chemokine (C-X-C motif) ligand (*CXCL*) 10 and *CXCL11*], and type 2 response genes [beta-galactoside alpha-2,6-sialyltransferase (*ST6GAL*) 1, periostin (*POSTN*), chloride channel accessory (*CLCA*) 1, carboxypeptidase A (*CPA*) 3, and interleukin 1 receptor like (*IL1RL*) 1]. The detailed information regarding

demographic and clinical characteristics of those subjects are unavailable.

Immunohistochemistry

Inferior turbinate tissue samples were fixed in 4% formaldehyde solution and embedded in paraffin. Paraffin sections (4 μ m) were prepared from paraffin-embedded human tissue samples. After deparaffinization and rehydration, sections were stained with hematoxylin and eosin routinely to determine the general pathologic features. Immunohistochemical staining was performed as previously reported.^{S9-11} Sections were subjected to heat-induced epitope retrieval using citric acid repair solution (Guge Biotechnology, Wuhan, China). The 3% hydrogen peroxidase (Boster Biotechnology, Wuhan, China) was used for endogenous peroxidase inhibition and 5% bovine serum albumin (Guge Biotechnology) was used to block nonspecific binding. Sections were stained with the primary antibody against ACE2 (ab108252, 1:100, Abcam, Cambridge, UK) overnight at 4°C. Species- and subtype-matched antibody was used as a negative control. Antigen was detected by using the streptavidin-peroxidase complex method with a histostain-plus kit (Boster Biotechnology) according to the manufacturer's instructions. Color development was achieved with 3', 3'-diaminobenzidine, which rendered positive cells brown. Sections were counterstained with hematoxylin and mounted. The intensity of positive staining in epithelium was analyzed by using image pro-plus 6.0 analysis software (Media Cybernetics, Inc. Silver Spring, MD, USA) and the results were presented as mean optical density value per unit area.^{S12}

Human nasal epithelial cell culture and treatment

HNECs were collected by epithelial scrapings of inferior turbinate from subjects without AR (n = 6), and then cultured with an air-liquid interface (ALI) method as mentioned elsewhere.^{S13} Briefly, the HNECs obtained during surgery were washed twice in Dulbecco modified Eagle medium (Thermo Fisher Scientific, Waltham, MA, USA) with penicillin/streptomycin and then grown submerged in bronchial epithelial cell basal medium (BEBM, Lonza, Walkersville, MD, USA) supplemented with SingleQuot Kit Suppl (Lonza) in 6-well plates coated with rat tail collagen type I (Sigma-Aldrich, St. Louis, MO, USA) in a 5% CO₂-humidified atmosphere at 37°C. Upon confluence, the cells were passaged to gel-coated transwell culture inserts (0.4 µm pore size; Becton Dickison, Franklin Lake, NJ, USA) and were grown in bronchial epithelial cell growth medium (Lonza). When they were confluent, medium from the apical side of the culture was removed and medium below the insert was replaced with an air-liquid interface medium consisting of BEBM/Dulbecco's modified Eagle's medium H (50: 50; Invitrogen). HNECs were maintained at ALI culture for 21 days for the differentiation. After the HNECs were differentiated, they were stimulated with interleukin (IL)-1β, tumor necrosis factor (TNF) α, IL-4, IL-13, IL-17A, IFN-γ, IL-33, and thymic stromal lymphopoietin (TSLP) at 10 ng/mL (R&D systems, Minneapolis, MN, USA), 10⁻⁷ M dexamethasone (Sigma-Aldrich, St. Louis, MO, USA), poly (I:C) (dsRNA) at 25 µg/mL (Tocris, Bristol, UK), lipopolysaccharides (LPS) (InvivoGen, San Diego, CA, USA) at 1 µg/mL, staphylococcal enterotoxin B (SEB) (Millipore, Merck KGaA, Darmstadt, Germany) at 1 µg/mL or the combination of IL-13 with IL-17A, IL-13 with IFN-γ, IL-17A with IFN-γ, or IL-13 with IL-17A and IFN-γ at a dose

mentioned above for 6 hours. After stimulation, cells were harvested for quantitative RT-PCR assay.^{S10}

Quantitative RT-PCR

Total RNA was extracted from tissue samples and cultured HNECs by using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) as mentioned elsewhere.^{S10,11} A total of 1 µg RNA was reverse-transcribed to cDNA using a PrimeScript RT reagent kit (TaKaRa Biotechnology, Dalian, China). cDNA equivalent to 50 ng of total RNA was used for PCR assay. Quantitative PCR was performed by using the SYBR Premix Ex Taq kit (TaKaRa Biotechnology) with specific primers (Table S2) on StepOnePlus (Applied Biosystems, Foster City, CA, USA). Beta-glucuronidase (GUSB) was used as a housekeeping gene for normalization of gene expression. No template sample was used as negative control. Amplification was as follows: 95 °C for 2 min, followed by 40 cycles of 95 °C for 10 sec, specific annealing temperature for 10 sec, and 72 °C for 15 sec. After PCR, a melting curve was constructed by increasing the temperature from 65 to 95 °C with a temperature transition rate of 0.1°C/s. Relative gene expression was calculated by using the 2(-Delta Delta CT) method.^{S14} A normal inferior turbinate mucosal sample and a control cell culture sample were used as the calibrator for tissue samples and cell culture samples, respectively.

Statistical analysis

For tissue and cell expression data, data are expressed as medians and interquartile ranges. For continuous variables, data distribution was tested for normality using a

Kolmogorov-Smirnov test or a Shapiro-Wilk test. Since variables were not normally distributed, a Mann-Whitney *U* 2-tailed test was used for between-group comparison.^{S3} For categorical variables, Chi-square or Fisher's exact test was applied to compare the difference in proportions between groups when appropriate. Multivariate logistic regression was used to adjust the confounding factors in comparison between AR and non-AR patients. The variables potentially confounding the association between AR comorbidity and COVID-19 were further addressed by using the propensity score-matching (PSM) method. Exact matching with a caliper size of 0.05 was applied for all matching pairs according to the propensity scores. Cell culture data are expressed as mean $\pm$ SEM and analyzed by unpaired Student's *t* test. Significance was accepted at a *P* value less than 0.05. Statistical analyses were performed by using GraphPad Prism software (GraphPad Inc, La Jolla, USA) or an IBM SPSS 22.0 package (SPSS Inc, Chicago, IL).

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Table S1. Demographic and characteristics of patients in immunohistochemistry, RT-PCR, and cell culture study.

	Control	AR	<i>P value</i>
Total subjects enrolled	29	29	
Methodology used			
<i>RT-PCR</i>			
Subject number, N	19	19	
Gender, male, N (%)	13 (68.4%)	12 (63.2%)	0.99
Age (years), median (IQR)	26 (19, 43)	34 (24, 38)	0.68
Patients with asthma, N (%)	0 (0%)	1 (5.3%)	0.99
<i>Immunohistochemistry</i>			
Subject number, N	10	10	
Gender, male, N (%)	7 (70%)	8 (80%)	0.99
Age (years), median (IQR)	34 (23, 48)	44 (31, 53)	0.32
Patients with asthma, N (%)	0 (0%)	1 (5.3%)	0.99
<i>Cell culture</i>			
Subject number, N	6	-	-
Gender, male, N (%)	4 (66.7%)	-	-
Age (years), median (IQR)	36 (21, 42)	-	-
Patients with asthma, N (%)	0 (0%)	-	-

For continuous variables, results are expressed as medians and interquartile ranges.

Categorical variables are summarized using percentage.

A Mann-Whitney U 2-tailed test was used for between-group comparison. For categorical variables, Chi-square or Fisher's exact test was applied to compare the difference in proportions between groups when appropriate.

AR, allergic rhinitis; IQR, interquartile ranges.

238 **Table S2. Primers used for quantitative RT-PCR analysis.**

Primer	Sequence	Annealing temperature (°C)	Expect product size (bp)
<i>ACE2</i>	(F)5'-ACAGTCCACACTTGCCCAAAT-3' (R)5'-TGAGAGCACTGAAGACCCATT-3'	60	103
<i>ST6GAL1</i>	(F)5'-ACCCCAATCAGCCCTTTTACA-3' (R)5'-CTGGTCACACAGCGTCATCA-3'	60	149
<i>POSTN</i>	(F)5'-GACCGTGTGCTTACACAAATTG-3' (R)5'-AAGTGACCGTCTCTTCCAAGG-3'	60	128
<i>CXCL10</i>	(F)5'-GTGGCATTCAAGGAGTACCTC-3' (R)5'-TGATGGCCTTCGATTCTGGATT-3'	60	198
<i>CXCL11</i>	(F)5'-GACGCTGTCTTTGCATAGGC-3' (R)5'-GGATTTAGGCATCGTTGTCCTTT-3'	60	148
<i>CCL26</i>	(F)5'-GGAAGTCCACACGTGGGAGTGAC-3' (R)5'-CTCTGGGAGGAAACACCTCTCC-3'	60	354
<i>GUSB</i>	(F)5'-GACACGCTAGAGCATGAGGG-3' (R)5'-GGGTGAGTGTGTTGTTGATGG-3'	60	121

239 ACE2, angiotensin-converting enzyme II; CXCL, chemokine (C-X-C motif) ligand;
 240 CCL, chemokine (C-C motif) ligand; POSTN: periostin; ST6GAL1: beta-galactoside
 241 alpha-2,6-sialyltransferase 1; GUSB, beta-glucuronidase.

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Table S3. Demographics and comorbidities of COVID-19 patients without and with AR before and after propensity matching of cohorts.

Demographics and comorbidities	Unmatched			Matched (1:1)		
	Without AR	With AR	<i>P</i> value	Without AR	With AR	<i>P</i> value
Subject, N	1,057	115	-	109	109	-
Gender, male, N (%)	511 (48.3)	66 (57.4)	0.08	56 (51.4)	62 (56.9)	0.50
Age, years, median (IQR)	61 (49, 69)	54 (40, 65)	<0.01	56 (42.5, 67)	55 (41, 65)	0.49
Smoking, N (%)	81 (7.7)	4 (3.5)	0.13	3 (2.8)	4 (3.7)	0.99
Any comorbidity, N (%)	-	-	-	-	-	-
Hypertension	344 (32.5)	28 (24.4)	0.07	25 (22.9)	26 (23.9)	0.99
Diabetes	149 (14.1)	13 (11.3)	0.41	7 (6.4)	11 (10.1)	0.46
Cardiovascular disease	97 (9.2)	11 (9.6)	0.87	13 (11.9)	10 (9.2)	0.66
Cerebrovascular disease	20 (1.9)	3 (2.6)	0.49	5 (4.6)	3 (2.8)	0.72
Malignancy	19 (1.8)	0 (0)	0.25	0 (0)	0 (0)	-
Chronic kidney disease	23 (2.2)	1 (0.9)	0.50	1 (0.9)	1 (0.9)	0.99
Chronic liver disease	12 (1.1)	5 (4.4)	0.02	4 (3.7)	2 (1.8)	0.68
CRS	62 (5.9)	10 (8.7)	0.22	6 (5.5)	10 (9.2)	0.44
Asthma	23 (2.2)	6 (5.2)	0.06	6 (5.5)	4 (3.7)	0.75
COPD	8 (0.8)	2 (1.7)	0.26	1 (0.9)	1 (0.9)	0.99

Data are presented as medians and interquartile ranges for continuous variables and numbers with percentage for categorical variables.

A Mann-Whitney *U* 2-tailed test was used for between-group comparison. For categorical variables, Chi-square or Fisher's exact test was applied to compare the difference in proportions between groups when appropriate.

Age, gender, smoking status, and all comorbidities were selected for propensity score matching.

COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; AR, allergic rhinitis; IQR, interquartile range.

254 **Table S4. Laboratory test results of COVID-19 patients without and with AR**
 255 **before and after propensity score matching.**

Characteristics	Unmatched		<i>P</i> value	Adjusted <i>P</i> value*	Matched (1:1) [#]		<i>P</i> value
	Without AR	With AR			Without AR	With AR	
Subject, N	1057	115	-	-	109	109	-
Laboratory tests, median (IQR)	-	-	-	-	-	-	-
Leucocytes count (×10 ⁹ /L)	5.5 (4.4, 7.0)	5.2 (3.9, 6.8)	0.08	0.10	5.7 (4.7, 7.8)	5.2 (3.9, 6.8)	0.07
Neutrophil count (×10 ⁹ /L)	3.8 (2.7, 5.3)	3.5 (2.6, 4.7)	0.12	0.15	4.0 (2.8, 5.3)	3.5 (2.7, 4.7)	0.06
Lymphocyte count (×10 ⁹ /L)	1.2 (0.9, 1.6)	1.3 (0.9, 1.6)	0.15	0.66	1.3 (0.9, 1.8)	1.3 (1.0, 1.6)	0.85
Eosinophil count (×10 ⁹ /L)	0.04 (0.01, 0.1)	0.06 (0, 0.1)	0.46	0.89	0.06 (0.01, 0.1)	0.06 (0.01, 0.12)	0.67
Alanine aminotransferase (U/L)	24 (15, 40)	25.5 (17, 46.5)	0.22	0.79	24 (17, 41)	25 (17.3, 44.8)	0.65
Aspartate aminotransferase (U/L)	23 (18, 35)	28 (19, 36.25)	0.04	0.67	23 (17, 35)	28 (19.3, 35.8)	0.07
Albumin (g/L)	35.9 (32.6, 39.6)	37.1 (33.0, 40.5)	0.14	0.96	36.1 (33.2, 40.8)	37.1 (33.1, 40.6)	0.51
Creatinine (umol/L)	67 (56, 81)	69.5 (58.75, 83)	0.19	0.15	65.5 (55.3, 78.5)	70 (59.3, 83)	0.13
Urea (umol/L)	4.2 (3.3, 5.4)	4.1 (3.2, 5.1)	0.45	0.33	4.3 (3.1, 5.5)	4.1 (3.2, 5.1)	0.72
Cardiac troponin I (pg/mL)	3.4 (1.9, 7.3)	2.3 (1.9, 5.8)	0.01	0.77	3.5 (1.9, 7.6)	2.3 (1.9, 5.8)	0.12
Procalcitonin (ng/mL)	0.05 (0.03, 0.07)	0.06 (0.03, 0.07)	0.90	0.50	0.05 (0.03, 0.08)	0.05 (0.03, 0.07)	0.68
Ferritin (μg/mL)	517.8 (304.5, 866.1)	585.3 (360.7, 943.6)	0.28	0.49	582 (401.8, 963.2)	590 (369.5, 899.1)	0.85
Erythrocyte sedimentation (mm/H)	31 (14, 58.5)	24.5 (12.75, 42.25)	0.04	0.10	27.5 (9, 45)	22.5 (12, 40.5)	0.66
D-D dimers (μg/mL)	0.63 (0.33, 1.38)	0.57 (0.27, 1.01)	0.06	0.09	0.52 (0.28, 1.13)	0.56 (0.27, 1.01)	0.98
Fibrin (g/L)	4.6 (3.6, 5.8)	4.3 (3.6, 5.4)	0.28	0.51	4.3 (3.3, 5.6)	4.3 (3.6, 5.4)	0.78
IL-6 (pg/mL)	4.7 (2.0, 17.2)	3.3 (1.8, 10.2)	0.08	0.15	4.0 (2.0, 11.7)	3.3 (1.8, 9.8)	0.42
IL-8 (pg/mL)	9.2 (5.5, 16.7)	10.2 (5.1, 20.1)	0.55	0.54	8.4 (5.1, 14.7)	10.2 (5.1, 20.0)	0.24

256 Data are presented as medians and interquartile ranges for continuous variables.

257 *In adjusted logistic regression analysis, adjusted variables included age, gender,
 258 smoking, and comorbidities (hypertension, diabetes, cardiovascular disease
 259 cerebrovascular diseases, malignancy, chronic liver diseases, chronic kidney diseases,
 260 chronic rhinosinusitis, asthma, and chronic obstructive pulmonary disease).

261 [#] Age, gender, smoking status, and all comorbidities were selected for propensity score

matching. Please see Table S3.

A Mann-Whitney U 2-tailed test was used for between-group comparison.

AR, allergic rhinitis; IL, interleukin; COVID-19, coronavirus disease 2019; IQR, interquartile range.

FIGURE LEGENDS

Figure S1. Interferon (IFN) and type 2 response genes expression in inferior turbinate tissues. A and B, The mRNA expression level of IFN response gene *CXCL10* and *CXCL11* (**A**) and type 2 response gene *ST6GAL1*, *POSTN* and *CCL26* (**B**) in inferior turbinate tissues from AR patients and controls as detected by quantitative RT-PCR. Control, n = 19; AR, n = 19. The Mann-Whitney *U* 2-tailed test was used for between-group comparison. ACE2: angiotensin-converting enzyme II; AR: allergic rhinitis; CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; ST6GAL1: beta-galactoside alpha-2,6-sialyltransferase 1; POSTN: periostin.

Figure S2. The correlations between *ACE2* gene expression and interferon (IFN) response gene and type 2 response gene expression in inferior turbinate tissues from controls or AR patients. A and B, The correlations between *ACE2* mRNA expression and the mRNA expression of IFN response genes (*CXCL10* and *CXCL11*), and type 2 response genes (*ST6GAL1*, *POSTN*, and *CCL26*) in inferior turbinate tissues from controls (**A**) and AR patients (**B**) were assessed separately. Control, n = 19; AR, n = 19. Spearman's correlation was used for correlation analysis. ACE2: angiotensin-converting enzyme II; AR: allergic rhinitis; CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; ST6GAL1: beta-galactoside alpha-2,6-sialyltransferase 1; POSTN: periostin.

Figure S3. *ACE2* gene expression positively correlates the expression of interferon

(IFN) response genes in nasal brushing epithelial cells. **A**, *ACE2*, type 2 response gene (*ST6GAL1*, *POSTN*, *CLCA1*, *CPA3*, and *IL1RL1*), and IFN response gene (*IFI6*, *CXCL10*, and *CXCL11*) expression in nasal brushings from patients with concomitant AR and asthma and healthy controls were profiled by RNA sequencing. Data was extracted from the public database GSE101720 and analyzed. Control, n = 9; AR with asthma, n = 7. **B**, The correlations between *ACE2* expression and *IFI6*, *CXCL10*, *CXCL11*, *ST6GAL1*, *POSTN*, *CLCA1*, *CPA3*, and *IL1RL1* expression in nasal brushings were assessed when analyzing controls and patients with AR and asthma together (n = 16). The Mann-Whitney *U* 2-tailed test was used for between-group comparison. Spearman's correlation was used for correlation analysis. **P* < 0.05 and ***P* < 0.01. *ACE2*: angiotensin-converting enzyme II; AR: allergic rhinitis; CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; IFI6: interferon alpha inducible protein 6; ST6GAL1: beta-galactoside alpha-2,6-sialyltransferase 1; POSTN: periostin; CLCA1: chloride channel accessory 1; CPA3: carboxypeptidase A3; IL1RL1: interleukin 1 receptor like 1.

Figure S4. The correlations between *ACE2* gene expression and interferon (IFN) response gene and type 2 response gene expression in nasal brushings from controls or patients with concomitant AR and asthma. A and B, *ACE2*, type 2 response gene (*ST6GAL1*, *POSTN*, *CLCA1*, *CPA3*, and *IL1RL1*), and IFN response gene (*IFI6*, *CXCL10*, and *CXCL11*) expression in nasal brushings from patients with concomitant AR and asthma and healthy controls were profiled by RNA sequencing.

Data was extracted from the public database GSE101720 and analyzed. The correlations between *ACE2* expression and *IFI6*, *CXCL10*, *CXCL11*, *ST6GAL1*, *POSTN*, *CLCA1*, *CPA3*, and *IL1RL1* expression in nasal brushings from healthy controls (**A**) and patients with concomitant AR and asthma (**B**) were assessed separately. Control, n = 9; AR with asthma, n = 7. Spearman's correlation was used for correlation analysis. ACE2: angiotensin-converting enzyme II; AR: allergic rhinitis; CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; IFI6: interferon alpha inducible protein 6; ST6GAL1: beta-galactoside alpha-2,6-sialyltransferase 1; POSTN: periostin; CLCA1: chloride channel accessory 1; CPA3: carboxypeptidase A3; IL1RL1: interleukin 1 receptor like 1.

Figure S5. *ACE2* gene expression positively correlates type 2 inflammation response gene expression in bronchial brushing epithelial cells. **A**, *ACE2*, type 2 response gene (*ST6GAL1*, *POSTN*, *CLCA1*, *CPA3*, and *IL1RL1*), and IFN response gene (*IFI6*, *CXCL10*, and *CXCL11*) expression in bronchial brushings from patients with concomitant AR and asthma and healthy controls were profiled by RNA sequencing. Data was extracted from the public database GSE101720 and analyzed. Control, n = 9; AR with asthma, n = 7. **B**, The correlations between *ACE2* expression and *IFI6*, *CXCL10*, *CXCL11*, *ST6GAL1*, *POSTN*, *CLCA1*, *IL1RL1*, and *CPA3* expression in bronchial brushings were assessed when analyzing controls and patients with AR and asthma together (n = 16). The Mann-Whitney *U* 2-tailed test was used for between-group comparison. Spearman's correlation was used for correlation analysis. **P* < 0.05,

**** $P < 0.01$, and *** $P < 0.001$. ACE2: angiotensin-converting enzyme II; AR: allergic rhinitis; CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; IFI6: interferon alpha inducible protein 6; ST6GAL1: beta-galactoside alpha-2,6-sialyltransferase 1; POSTN: periostin; CLCA1: chloride channel accessory 1; CPA3: carboxypeptidase A3; IL1RL1: interleukin 1 receptor like 1.**

Figure S6. The correlations between *ACE2* gene expression and interferon (IFN) response gene and type 2 response gene expression in bronchial brushings from controls or patients with concomitant AR and asthma. A and B, *ACE2*, type 2 response gene (*ST6GAL1*, *POSTN*, *CLCA1*, *CPA3*, and *IL1RL1*), and IFN response gene (*IFI6*, *CXCL10*, and *CXCL11*) expression in bronchial brushings from patients with concomitant AR and asthma and healthy controls were profiled by RNA sequencing. Data was extracted from the public database GSE101720 and analyzed. The correlations between *ACE2* expression and *IFI6*, *CXCL10*, *CXCL11*, *ST6GAL1*, *POSTN*, *CLCA1*, *CPA3*, and *IL1RL1* expression in bronchial brushings from healthy controls (A) and patients with concomitant AR and asthma (B) were assessed separately. Control, n = 9; AR with asthma, n = 7. Spearman's correlation was used for correlation analysis. ACE2: angiotensin-converting enzyme II; AR: allergic rhinitis; CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; IFI6: interferon alpha inducible protein 6; ST6GAL1: beta-galactoside alpha-2,6-sialyltransferase 1; POSTN: periostin; CLCA1: chloride channel accessory 1; CPA3: carboxypeptidase A3; IL1RL1: interleukin 1 receptor like 1.

Figure S7. Nasal and bronchial epithelial cells show distinct expression levels of interferon (IFN) response genes and type 2 response genes in patients with concomitant AR and asthma. **A**, *ACE2*, *IFI6*, *CXCL10*, *CXCL11*, *ST6GAL1*, *POSTN*, *CLCA1*, *CPA3*, and *IL1RL1* expression in nasal and bronchial brushings from patients with concomitant AR and asthma were compared (n = 7). Data was extracted from the public database GSE101720 and analyzed. **B**, The ratios of expression of *CXCL10* and *CXCL11* to the expression of *ST6GAL1*, *POSTN*, *CLCA1*, *CPA3*, and *IL1RL1* expression in nasal and bronchial brushings were compared (n = 7). Paired student's test was used for between-group comparison. **P* < 0.05 and ***P* < 0.01. CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; IFI6: interferon alpha inducible protein 6; ST6GAL1: beta-galactoside alpha-2,6-sialyltransferase 1; POSTN: periostin; CLCA1: chloride channel accessory 1; CPA3: carboxypeptidase A3; IL1RL1: interleukin 1 receptor like 1.