

One in five patients with chronic spontaneous urticaria has IgE to tissue transglutaminase 2

To the Editor,

Chronic spontaneous urticaria (CSU) is a mast cell-mediated inflammatory skin disease characterized by itchy wheals and angioedema that occur for longer than 6 weeks. IgE antibodies to various autoantigens, for example, thyroperoxidase (TPO) and interleukin 24 (IL-24), are held to drive the occurrence of signs and symptoms in type I autoimmune CSU, also known as autoallergic CSU (aaCSU).^{1,2}

Expression of tissue transglutaminase 2 (TG2), the autoantigen in celiac disease, was demonstrated to be increased in lesional skin mast cells of CSU patients.³ Furthermore, serum TG2 activity has been proposed as a potential biomarker of CSU severity and response to treatment with omalizumab.⁴ Here, we assessed the levels of IgE directed against TG2 (IgE-anti-TG2) in CSU patients and the correlation of IgE-anti-TG2 with clinical and serological features of CSU.

We used a human IgE capture ELISA to quantify IgE-anti-TG2 levels in 160 CSU patients and 54 healthy control subjects. We compared CSU patients with high and low serum levels of IgE-anti-TG2 for differences in clinical features and laboratory markers (Table 1). The methodology including statistical tests is described in File S1.

Overall, CSU patients had significantly higher IgE-anti-TG2 serum levels as compared to healthy control subjects (Figure 1). Using a cut-off value of 77.7 AU, as determined by the 95th percentile of respective levels in sera of control subjects, 33 of 160 CSU patients (20.6%) had elevated IgE-anti-TG2 levels (median: 144.6 AU), whereas 79.4% had normal levels (median 7.0 AU, Figure 1). Elevated IgE-anti-TG2 levels were not linked to any demographic, clinical and laboratory features of CSU including the presence of additional, previously described aaCSU-related autoreactive IgE, that is, IgE-anti-TPO and IgE-anti-IL-24 (Table 1 and Table S1).

TG2 and TG3 belong to a family of structurally and functionally related enzymes involved in post-translational modifications of proteins. TG2 along with TG3 are major autoantigens in celiac disease and dermatitis herpetiformis and are associated with the production

of TG-targeting IgA autoantibodies.⁵ Furthermore, TG3 is an autoallergen actively involved in skin inflammation in patients with atopic dermatitis, with higher levels of IgE-anti-TG3 as compared to healthy controls that correlate with disease activity.⁶

The rate of CSU patients with elevated levels of IgE-anti-TG2, that is, 21%, is lower than the rates previously reported for IgE-anti-IL-24 (80%)² and IgE-anti-TPO (54%–61%).¹ Future studies should assess the levels of IgE and IgG autoantibodies to all three antigens in the same patient population, ideally in a multicenter approach. Interestingly, the presence of IgE-anti-TG2 was not linked to elevated levels of IgE-anti-IL-24 or IgE-anti-TPO, suggesting that different subpopulations of autoallergic CSU patients exhibit distinct profiles of autoallergens targeted by their IgE.

Functional assays have to be performed to confirm that TG2 and IgE-anti-TG2 can activate and degranulate human skin mast cells. Recently, mast cells have been shown to release TG2, leading to enhanced IgE production in B cells by up-regulating CD40L expression.^{3,4} This suggests autocrine activation of mast cells by TG2-IgE-anti-TG2 crosslinking of FcεRI. Furthermore, further research should assess CSU patients' levels of IgE-anti-TG3, which were shown to be increased in patients.

Additional studies are needed to compare levels of IgE-anti-TG2 in different responders to omalizumab (fast, slow, non-responders) both at baseline and during follow-up. Finally, CSU patients are shown to have an increased risk of celiac disease and vice versa, and further studies should clarify whether the presence of IgE-anti-TG2 is associated with this risk.

In summary, a distinct and sizeable subpopulation of CSU patients shows increased IgE-anti-TG2 levels. The role of IgE-anti-TG2 and TG2 in the pathogenesis of CSU pathogenesis as well as their clinical relevance should be evaluated in further studies.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: Huichun Su, Scheffel Jörg, Xu Yao, and Sabine Altrichter; Performed the experiments: Huichun

Parameters	IgE-anti-TG2		p-Value
	Negative (n = 127)	Positive (n = 33)	
Female, % (n/total)	72.2 (91/126)	71.9 (23/32)	0.969
Age, years	41.0 (32.0–55.2)	41.5 (30.2–57.5)	0.770
Duration of disease, years	1.7 (1.0–5.0)	2.0 (0.8–6.7)	0.863
Presence of angioedema, % (n/total)	71.5 (88/123)	62.1 (18/29)	0.318
UAS7	15.0 (5.2–21.0)	13.0 (4.0–18.0)	0.443
UCT	8.0 (4.0–11.5)	7.0 (5.0–11.0)	0.925
DLQI	7.0 (3–12)	4.5 (1.5–8.7)	0.205
Positive skin prick tests to inhalant allergens, % (n/total)	47.4 (54/114)	65.5 (19/29)	0.081
Positive ASST, % (n/total)	42.6 (52/122)	48.4 (15/31)	0.564
Total serum IgE, kU/L	73.2 (22.7–214.7)	87.5 (30.1–204.5)	0.728
Total IgA, g/L	1.6 (1.1–2.1)	1.8 (1.4–2.2)	0.321
Total IgG, g/L	9.5 (7.8–11.9)	10.8 (9.6–11.7)	0.124
Total IgM, g/L	1.1 (0.8–1.7)	1.3 (0.8–1.8)	0.772
Blood eosinophil counts, $\times 10^9/L$	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.721
Blood basophil counts, $\times 10^9/L$	0.03 (0.01–0.05)	0.02 (0.01–0.05)	0.639
C-reactive protein, mg/L	1.8 (0.5–4.9)	2.2 (0.9–8.2)	0.297
ESR, mm/h	8.0 (3.0–16.5)	14.0 (6.0–20.0)	0.303
IgG-anti-TPO, kU/L	10.0 (5.0–17.0)	10.0 (8.0–18.0)	0.298
IgE-anti-TPO total, AU	8.1 (6.4–13.3)	6.5 (5.9–14.5)	0.173
IgE-anti-TPO free, AU	1.1 (0.9–1.4)	1.1 (0.8–2.0)	0.928
IgE-anti-IL-24 total, AU	4.5 (3.8–6.0)	4.6 (3.3–5.6)	0.513
IgE-anti-IL-24 free, AU	3.9 (3.1–4.6)	3.6 (3.0–4.8)	0.370
C3 complement, mg/L	123 (87–126)	128 (109–148)	0.173
C4 complement, mg/L	33.0 (21.5–38.5)	36.0 (22.0–40.0)	0.809

Note: Values are given as median (interquartile range).

Abbreviations: ASST, autologous serum skin test; AU, arbitrary units; C3, complement 3; C4, complement 4; DLQI, Dermatology Life Quality Index; ESR, erythrocyte sedimentation rate; IL, Interleukin; TPO, thyroperoxidase; UAS7, urticarial activity score over 7 days; UCT, urticaria control test.

TABLE 1 Comparison of parameters between IgE-anti-TG2-negative and IgE-anti-TG2-positive CSU patients.

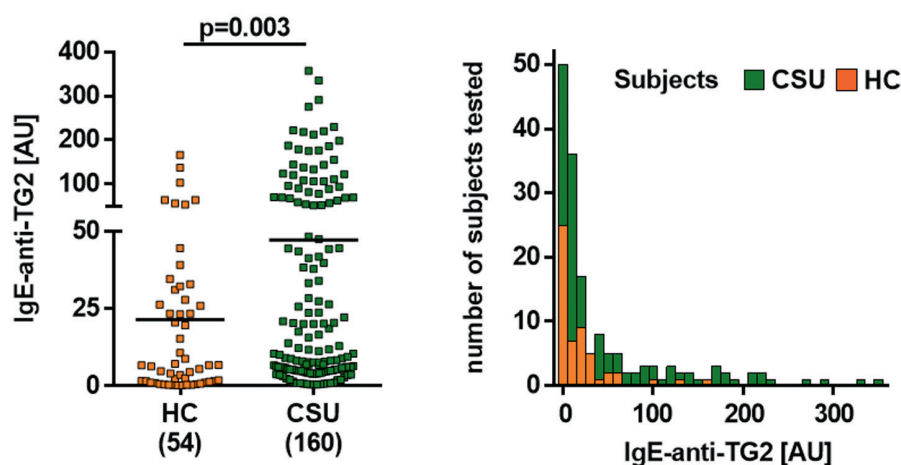


FIGURE 1 Patients with chronic spontaneous urticaria exhibit elevated levels of IgE-anti-TG2. (Left) Healthy control subjects (HC) exhibit median IgE-anti-TG2 levels of 6.7 arbitrary units (AU), IQR 1.3–28.7 AU. The highest value in HC was 166.3 AU. CSU patients showed median IgE-anti-TG2 levels of 10.8 AU, IQR 5.0–58.5 AU, and the highest value was 356.9 AU. Fifteen CSU patients (9.4%) showed levels of IgE-anti-TG2 higher than 166.3 AU (175.25–356.99 AU). The groups were compared using the Mann–Whitney U test. (Right) A histogram displays the distribution of IgE-anti-TG2 levels in CSU patients and HC. CSU patients can be divided into IgE-anti-TG2 negative group (n = 127, median 7.0 AU, IQR: 4.6–20.9 AU) and IgE-anti-TG2 positive group (n = 33, median: 144.6 AU, IQR: 107.2–215.4 AU) based on 77.7 AU cutoff.

Su; Analyzed the data: Pavel Kolkhir, Huichun, Su; Wrote the paper: Huichun Su, Sabine Altrichter, Pavel Kolkhir, Marcus Maurer. Data for IgE anti-TPO, IgG anti-TPO, and IgE anti-IL-24: Yi-Kui Xiang; Statistical analysis: Pavel Kolkhir, Huichun Su.

FUNDING INFORMATION

Natural Science Foundation of Fujian Province (2019J01310), Intramural funds of Fujian Medical University Union Hospital (2021XH026).

CONFLICT OF INTEREST STATEMENT

Huichun Su: No conflicts of interest regarding any aspects of this study. Pavel Kolkhir: No conflicts of interest regarding any aspects of this study. Jörg Scheffel: No conflicts of interest regarding any aspects of this study. Yi-Kui Xiang: No conflicts of interest regarding any aspects of this study. Xu Yao: No conflicts of interest regarding any aspects of this study. MM is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Aralez, Genentech, GSK, Menarini, Merckle Recordati, Moxie, Novartis, Sanofi, MSD, and Uriach. SA is or recently was a speaker and/or advisor for and/or has received research funding from AstraZeneca, Allakos, CSL Behring, Sanofi, Takeda, ThermoFisher, Moxie, and Novartis.

ACKNOWLEDGEMENT

Open Access funding enabled and organized by Projekt DEAL.

Huichun Su^{1,2,3} 
 Pavel Kolkhir^{1,2} 
 Jörg Scheffel^{1,2} 
 Yi-Kui Xiang^{1,2} 
 Xu Yao⁴ 
 Marcus Maurer^{1,2} 
 Sabine Altrichter^{1,5} 

¹Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

²Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany

³Department of Dermatology, Fujian Medical University Union Hospital, Fuzhou, China

⁴Institute of Dermatology, Chinese Academy of Medical Sciences

and Peking Union Medical College, Nanjing, China

⁵Department of Dermatology and Venerology, Kepler University Hospital, Linz, Austria

Correspondence

Marcus Maurer, Institute for Allergology, Charité – Universitätsmedizin Berlin, Hindenburgdamm 30, 12203 Berlin, Germany.

Email: marcus.maurer@charite.de

ORCID

Huichun Su  <https://orcid.org/0000-0002-0980-0675>
 Pavel Kolkhir  <https://orcid.org/0000-0001-5380-8132>
 Jörg Scheffel  <https://orcid.org/0000-0002-9365-3785>
 Yi-Kui Xiang  <https://orcid.org/0000-0003-3432-6837>
 Xu Yao  <https://orcid.org/0000-0003-3509-4775>
 Marcus Maurer  <https://orcid.org/0000-0002-4121-481X>
 Sabine Altrichter  <https://orcid.org/0000-0001-9955-385X>

REFERENCES

- Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase—a novel pathomechanism of chronic spontaneous urticaria? *PLoS One*. 2011;6:e14794. doi:10.1371/journal.pone.0014794
- Schmetzer O, Lakin E, Topal FA, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2018;142:876-882. doi:10.1016/j.jaci.2017.10.035
- Hong GU, Ro JY, Bae Y, et al. Association of TG2 from mast cells and chronic spontaneous urticaria pathogenesis. *Ann Allergy Asthma Immunol*. 2016;117:290-297. doi:10.1016/j.anai.2016.06.026
- Bae Y, Kang SH, Park JO, Park G-H, Choi J-H. Serum transglutaminase 2 activity as a potential biomarker of disease severity and response to omalizumab in chronic spontaneous urticaria. *Allergol Int*. 2020;69:304-306. doi:10.1016/j.alit.2019.10.009
- Kárpáti S, Sárdy M, Németh K, et al. Transglutaminases in autoimmune and inherited skin diseases: the phenomena of epitope spreading and functional compensation. *Exp Dermatol*. 2018;27:807-814. doi:10.1111/exd.13449
- Su H, Luo Y, Sun J, et al. Transglutaminase 3 promotes skin inflammation in atopic dermatitis by activating monocyte-derived dendritic cells via DC-SIGN. *J Invest Dermatol*. 2020;140:370-379.e8. doi:10.1016/j.jid.2019.07.703

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.