

Correspondence

HαT is associated with increased risk for severe Hymenoptera venom-triggered anaphylaxis

To the Editor:

We read with great interest the recent review published in *The Journal of Allergy and Clinical Immunology* by Dr Joshua Boyce and covering recent advances in mast cell biology,¹ in which some of our work was highlighted.²

However, the description of our findings regarding the association of hereditary α -tryptasemia (HαT) with Hymenoptera venom-triggered anaphylaxis (HVA) was not consistent with our reporting and thus appeared to affect Boyce's conclusion that HαT is not associated with an increased risk for severe HVA.

In contrast to Boyce's reporting of our results, our cited study,² in which 374 consecutive patients with Hymenoptera allergy were prospectively screened for *KIT* p.D816V, found that HαT was approximately twice as common among patients with severe HVA; specifically, 7.3% of individuals with grade IV (Mueller scale) HVA ($n = 11$ of 150) were found to have HαT versus 3.6% of those with grade I to III HVA or large local reactions ($n = 8$ of 224).² This study was neither designed nor powered to detect a difference in the prevalence of HαT. However, the odds ratio (OR) of 2.1 was comparable to that in a larger retrospective study by Lyons et al, which was powered for such analysis (OR = 2.2).³ This previous study also found that HαT is significantly more prevalent among patients with idiopathic anaphylaxis and associated with a significantly increased prevalence of anaphylaxis among individuals with systemic mastocytosis (SM), in which case HVA was approximately twice as common among patients with SM and HαT. In a 2020 report by Greiner et al in the journal *Blood*,⁴ HαT was also found to be associated with an approximately 3- to 4-fold increase in the prevalence of "severe cardiovascular mediator-related symptoms (mainly anaphylaxis)" resulting predominantly from Hymenoptera envenomation. Because the diagnosis of HVA and severity grading were adjudicated by 3 independent investigators in the retrospective study³ and in both that study and our cited study² the same investigators and study population (ie, patients sent to the only tertiary referral center in the country for evaluation of venom allergy) were involved, one could reasonably combine the results of the 2 studies. When this is done, of the 881 evaluated individuals with venom allergy, a total of 8.4% of all of those individuals

with grade IV HVA ($n = 32$ of 379) were found to have HαT versus 4.0% of those with grade I to III HVA or large local reactions ($n = 20$ of 502) (Table I) ($P = .006$; OR = 2.2 [95% CI = 1.21-4.17]). However, it is critical to note that an increased prevalence of HαT was observed *only* among individuals with severe anaphylaxis (grade IV); the overall prevalence of HαT among the entire combined cohorts of patients with Hymenoptera venom allergy (5.9% [$n = 52$ of 881]) was no different from those reported for the general populations of the United Kingdom, United States, and European Union. Thus, HαT does not appear to contribute to the development of Hymenoptera allergy but instead modifies the severity of reactions among patients with venom allergy.

We agree that statements regarding the potential impact of HαT on other forms of anaphylaxis should remain guarded at this time. However, the evolving data suggest that HαT may modify mast cell-mediated reactions in additional settings. These data include a series of observations made by Le et al in the *Journal of Experimental Medicine*⁵ and Lyons et al in the *Journal of Allergy and Clinical Immunology*,³ in which mature α/β -tryptase heterotetramers were initially described, found to increase with higher relative numbers of α -tryptase-encoding gene copy, and shown to have increased stability and expanded substrate specificity. α/β -Tryptase heterotetramers were shown to be uniquely able to cleave the mechanosensing GPCR EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2) and protease-activated receptor 2 (PAR2). Such activity was associated with increased endothelial cell leak and mast cell activation in response to vibration *in vitro*. And symptom response scores in patients and healthy volunteers following vibratory challenge *in vivo*.

Although our understanding of HαT and the complexity of the human tryptase locus continues to evolve, certain associations are coming into focus. HαT has consistently been linked to severe HVA, and this association appears to be independent of concomitant SM, helping to explain the historical association between elevated BST and severe HVA.^{2,3} How this knowledge will ultimately help guide medical decision making and anticipatory guidance in the future continues to require additional study.

Julij Šelb, MD, PhD^{a,b}
Matija Rijavec, PhD^{a,c}
Peter Kopač, MD, PhD^{a,b}
Jonathan J. Lyons, MD^d
Peter Korošec, PhD^{a,e}

TABLE I. Prevalence of HαT among individuals with HVA

	Grade IV HVA HαT	No-grade IV HVA HαT	OR [95% CI]; <i>P</i> value*
Lyons et al ³	21 of 229 (9.2%)	12 of 278 (4.3%)	2.2 [1.02-5.11]; .03
Šelb et al ²	11 of 150 (7.3%)	8 of 224 (3.6%)	2.1 [0.76-6.27]; .15
Combined ^{2,3}	32 of 379 (8.4%)	20 of 502 (4.0%)	2.2 [1.21-4.17]; .006

Boldface indicates combined cohorts.

*According to the Fisher exact test.

From ^athe University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia; ^bthe Medical Faculty, ^cthe Biotechnical Faculty, and ^ethe Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia; and ^dthe Translational Allergic Immunopathology Unit, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. E-mail: peter.korosec@klinika-golnik.si.

Supported in part by the Slovenian Research Agency (P3-0360) and the Division of Intramural Research of the National Institute of Allergy and Infectious Diseases, National Institutes of Health. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Boyce JA. Advances in mast cell biology. *J Allergy Clin Immunol* 2022;149:1919-25.
2. Šelb J, Rijavec M, Eržen R, Zidarn M, Kopač P, Škerget M, et al. Routine KIT p.D816V screening identifies clonal mast cell disease in patients with Hymenoptera allergy regularly missed using baseline tryptase levels alone. *J Allergy Clin Immunol* 2021;148:621-6.e7.
3. Lyons JJ, Chovanec J, O'Connell MP, Liu Y, Šelb J, Zanotti R, et al. Heritable risk for severe anaphylaxis associated with increased α -tryptase–encoding germline copy number at TPSAB1. *J Allergy Clin Immunol* 2021;147:622-32.
4. Greiner G, Sprinzel B, Górski A, Ratzinger F, Gurbisz M, Witzneder N, et al. Hereditary α tryptasemia is a valid genetic biomarker for severe mediator-related symptoms in mastocytosis. *Blood* 2021;137:238-47.
5. Le QT, Lyons JJ, Naranjo AN, Olivera A, Lazarus RA, Metcalfe DD, et al. Impact of naturally forming human α/β -tryptase heterotetramers in the pathogenesis of hereditary α -tryptasemia. *J Exp Med* 2019;216:2348-61.

<https://doi.org/10.1016/j.jaci.2022.11.017>