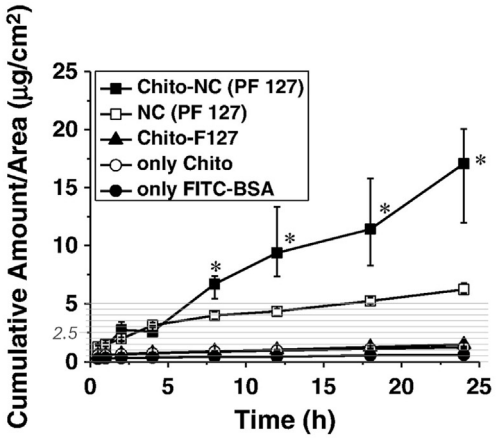
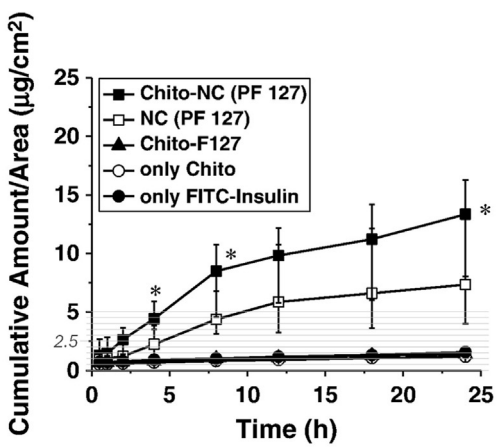
A



B



C

	Area of skin treated (cm^2)	Concentration of solution applied on skin (mg/ml)	Volume of solution applied on skin (µl)	Mass applied on skin (µg) [a]	Cumulative amount/area (µg/cm^2) [b, c]	Mass permeated (µg) [d]	Percent delivered [e]
FITC-BSA	0.636	1	200	200	0.5	0.32	0.2
FITC-Insulin	0.636	1	200	200	1.5	0.95	0.5

[a] Concentration of solution applied on skin x Volume of solution applied on skin

[b] FITC-BSA value read from Figure 1A for "only FITC-BSA" at 24 h

[c] FITC-Insulin value read from Figure 1B for "only FITC-Insulin" at 24 h

[d] Cumulative amount/area x Area of skin treated

[e] Mass permeated / Mass applied on skin * 100

FIG 1. Calculation of percentage of protein delivered. **A,** Data used for calculating percentage of delivery of BSA. **B,** Data used for calculating percentage of delivery of insulin. **C,** Calculation of percentage of delivery for BSA and insulin. Horizontal lines have been added to aid in reading values of fluorescein isothiocyanate (FITC)-BSA only and FITC-insulin only. The other treatment groups shown are not relevant to the current discussion. Reproduced from Choi et al[3] with permission of the publisher.

and anti PT-IgG titers. The microperforations increase skin permeability, allowing even Viaskin patches containing a low antigen dose to be used effectively. Microneedles carrying antigen doses in these amounts have been used successfully for vaccinations and allergen immunotherapy. Thus, because microneedles help in overcoming the skin barrier, the fraction of Viaskin patch dose that enters the skin may provide useful context for estimating a microneedle dose for allergen immunotherapy.

DISCLOSURE STATEMENT

Supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (awards R01AI135197 and R01AI121322 [both to H.S.G.]), and the Ronald B. and Cynthia J. McNeill Term Professorship in Nanomedicine (NC State University).

Disclosure of potential conflict of interest: H. S. Gill is a coinventor on a patent related to the use of microneedle technology for allergen immunotherapy and is also a cofounder and shareholder of Moonlight Therapeutics, a startup engaged in developing microneedles for allergen immunotherapy. These potential conflicts of interests have been disclosed and are being managed by NC Sate University.

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https://doi.org/10.1016/j.jaci.2025.01.039

First description of familial hypertryptasemia

To the Editor:

We have carefully reviewed the recent workshop summary published by Castells et al and titled, "Mast cell activation syndrome: Current understanding and research needs."[1] We believe that it is a thorough and insightful review, providing a comprehensive and up-to-date overview of the current understanding of mast cell activation syndrome. The rigorous design and appropriate balance between the description of previous results and those shown by the authors are the review's strengths, making it an essential read for researchers and clinicians who are involved in this area of study and seeking to improve patient care. However, we would like to highlight 1 key point that should be emphasized.

In their workshop summary, Castells et al[1] indicate that hereditary α-tryptasemia (HαT) is a recently described genetic trait, citing a study published by Lyons et al in 2016,[2] which associated increased *TPSAB1* copy numbers with symptoms suggestive of mast cell mediator release in different families. It is worth noting that since 2002, Professor Dávila had been following a female patient with recurrent episodes of hypotension, abdominal pain, nausea, and other symptoms, who maintained elevated tryptase levels that did not increase with the episodes. The diagnosis of mastocytosis was discarded after a bone marrow study with a

negative result. During the follow-up, he thought that persistent tryptase levels could be of familial origin, by analogy with familial hyperamylasemia.[3] After receiving permission to evaluate her sister and 2 daughters, he showed that all 3 had elevated tryptase levels, whereas the husband had normal levels. Our research group performed an extensive analysis of the *TPSAB1* gene,[4] which was the object of the doctoral dissertation of Dr Laura Hernandez that was published in 2013.[5] In this publication, we identified high *TPSAB1* mRNA expression levels correlated with baseline serum tryptase levels, suggesting its connection with the phenotype. In conclusion, to our knowledge, we have described for the first time the existence of a nosologic entity for which we suggest the term *familial hypertryptasemia* and in which different members of the same family had elevated levels of tryptase without mastocytosis.

Castells et al[1] provide valuable insights into the knowledge of HαT genotyping and associated clinical features, highlighting the implications of HαT for clinical practice. However, it should be noted that Dávila et al[1] played a significant role in the early description of familial hypertryptasemia, providing initial insight into the disease, as reported in the aforementioned doctoral thesis published in 2013.[5]

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: I. Dávila has received payment for lectures, including for service on speaker's bureaus, from Allergy Therapeutics, AstraZeneca, Chiesi, Diater, GSK, Leti, Novartis, and Sanofi; payment for a consultancy from Allergy Therapeutics, ALK-Abelló, AstraZeneca, GSK, Merck, MSD, Novartis, and Sanofi; and grants for Thermo Fisher Diagnostics. The rest of authors declare that they have no relevant conflicts of interest.

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https://doi.org/10.1016/j.jaci.2025.01.041

Reply

To the Editor:

We thank Dávila et al very much for pointing toward an early recognition of tryptase levels and gene involvement in mast cell activation symptoms and anaphylaxis. The description of a patient with episodes of anaphylaxis, who was followed since 2002, had an elevated baseline tryptase level; a negative bone marrow testing result for mastocytosis; and 3 family members with elevated baseline tryptase fit an autosomal dominant transmission of human tryptase alpha/beta1 gene (*TPSAB1)* replication.[1] We reviewed the elegant doctoral dissertation work in which increased *TPSAB1* mRNA correlated with elevated baseline serum tryptase levels, and we want to acknowledge the early findings presented in this 2013 dissertation. The description of the family is certainly consistent with hereditary alpha-tryptasemia (HαT).

In our early work in 2011 (Hamilton et al[2]), we provided the first standardized description of mast cell activation syndrome indicating that tryptase level elevations were associated with symptoms of mast cell activation, including anaphylaxis. We found that the mean baseline tryptase level was 10.7 ng/mL, with 5 of the 18 patients having levels higher than 8 ng/mL, likely representing HαT, which had not yet been discovered.[2]

Our first case series of 9 families with elevated serum tryptase levels inherited in an autosomal dominant manner was available online in its final accepted form in 2013, contemporaneously with the work by Dávila et al.[3] Several of those families had also been followed for several years at the National Institutes of Health and in Cincinnati before the publication, and they became the basis for the much larger publication describing *TPSAB1* replications causing HαT as the genetic change leading to these clinical findings, which were later reported in *Nature Genetics*.[4] Another report from Sabato et al[5] was also published online in the *Journal of Clinical Immunology* and available in mid-2018; the report described a family with "familial hypertryptasemia" that was followed for several years. This same family was also later confirmed to have HαT, becoming the first identified with a quintuplication of *TPSAB1*.[5]

We want to congratulate Dávila et al for their efforts toward further understanding the pathogenesis of mast cell activation disorders and anaphylaxis, as well as for looking into the correct direction, namely, tryptase levels and genes, the results of which were confirmed across the Atlantic, pushing the field forward. It is by replicating clinical observations and laboratory research that the field of medicine advances.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: M. Castells was supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), and has received research funding and consulting fees from Blueprint Medicines and consulting fees from Cogent Biosciences. The content is solely the responsibility of the authors and does not represent the official views of the NIH. The remaining author declares that he has no relevant conflicts of interest.

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