with elevated BST levels absent HαT or clonal mast cell disease (Fig 1, C).

Thus, although Chollet and Akin address an important question,1 their study cannot clarify phenotypic associations with HαT. Furthermore, conclusions regarding potential impacts of β-tryptase copy number on BST level are not justified. The clinical impact of HαT will certainly be refined by large well-designed studies in the future. However, we are still only beginning to perceive the full implications of tryptase genetic variability with regard to human health and disease.

I thank Allyson Mateja, MSPH, for her expertise in reviewing the statistical methods.

Jonathan J. Lyons, MD

From the Translational Allergic Immunopathology Unit, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. E-mail: jonathan.lyons@nih.gov.

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Reply

To the Editor:

We read the letter sent by Dr Lyons in response to our recent publication showing no clinical phenotypes associated with hereditary α-tryptasemia (HαT).1 We appreciate the careful analysis and comments provided by Dr Lyons, who was the first author of the original publication claiming that HαT is associated with a “multisystem disorder” associated with common and seemingly unrelated symptoms such as irritable bowel syndrome, cutaneous complaints, connective tissue abnormalities, and dysautonomia.2

In his letter,3 Dr Lyons states that our sample did not have the statistical power to reach the conclusion that HαT is not associated with these entities and studies in larger cohorts are needed. Although we agree and support studies in larger cohorts and although we acknowledged the sample size as a potential limitation in our article, we must point out that the statistical analysis used in our article, namely, the Fisher exact test, is valid for all sample sizes, including small sample sizes, and the conclusions are accurate for our sample. To that end, it is useful to remember the original HαT multisystem phenotype claims emerged from the article by Lyons et al, which used the same statistical test used in our article but was flawed in that a multiple comparison correction such as the Bonferroni correction was not used to adjust P values when the authors reported querying at least 12 unrelated symptoms.3 We note that the P values in that article were only marginally below the .05 cutoff level, and they would have easily become nonsignificant if a corrected P value had been used or if the significance level was more conservatively set at the .01 level. Consistent with these conclusions, Robey et al found that the prevalence of HαT was not increased in a population of 4283 patients referred for allergy evaluation; there was no difference in clinical symptoms between patients with α-tryptase gene duplications and patients with higher copy numbers, and there was no increase in hypermobility or dizzy spells suggestive of dysautonomia in their population.4 Similarly, there is no increase in HαT prevalence in patients with irritable bowel syndrome. Therefore, to date, there exist no compelling or reproducible data indicating that HαT is associated with a multisystem disorder phenotype.

Dr Lyons’ concerns regarding the clinic sample are also misplaced. A referral to evaluation for a mast cell disorder does not mean that all patients have the same set of symptoms or that their clinical condition is a foregone conclusion. For example, although some patients may have venom allergies, others may have chronic itching and urticaria, and still others may present with gastrointestinal symptoms that could have triggered their referral. We would also like to clarify the methodology used to recruit the clinic sample. All of the patients who were recruited had previously had a tryptase level determined. Tryptase level was used to help select the 50 consecutive patients without clonal mast cell disease with the goal of recruiting participants with a spectrum of tryptase levels both within and beyond the normal reference range. The fact that 41% of clinic participants had HαT reflects a selection based on tryptase level rather than an association between HαT and certain symptoms or clinical condition, and it only highlights the impact of selection bias when studying a referral population.

We would also like to respond to Dr Lyons’ suggestion to use a “validated symptom assessment tool” by stating that the article presenting this tool was also coauthored by one of us and reflects a consensus statement rather than a validation. The purpose of our study was not to examine a composite symptom severity score but rather to investigate the presence or absence of individual symptoms reported to be associated with HαT when the same questionnaire from the original study by Lyons et al was used.5 We should point out that one of the strengths of our study of our clinic patients was its prospective recruitment and that all patients answered the same set of questions. This is different from a retrospective or database review in which patients may have been evaluated by different clinicians and some symptoms may not have been questioned or entered into the database. Lastly, this survey accurately identified symptoms of mastocytosis as described in our Results section.

Dr Lyons also comments on our report of β-tryptase duplications, a finding that was first reported by us.6 Dr Lyons comments on different isoforms of the TPSB2 gene, and a conclusion could not be made regarding the impact of β-tryptase duplications on serum tryptase level. We should note that our study reports...
β-tryptase duplications only in the context of a possible confounder in patients with haplotypes showing greater than 3 β-tryptase genes (such as αβββ), as it cannot be ruled out that β-tryptase duplication could be responsible for this genotype. We made no claims or attempts to investigate different isotypes of the β-tryptase gene or their impact on serum tryptase levels. We believe that the impact of β-tryptase genes on measurable total serum tryptase remains to be investigated beyond the 2 pedigrees that Dr Lyons now reports in his letter. β-Tryptase genes can contribute to measurable tryptase in the serum through their secreted protryptase forms. In 2007, we published a report showing no difference in elevated basal serum tryptase levels in patients with mastocytosis who lack α-tryptase. We have also recently evaluated a patient with 5 β-tryptase genes and no α-tryptase gene who had a baseline tryptase level of 13.1 ng/mL. Moreover, although Dr Lyons claims that β-tryptase duplications have been reported before, we have reviewed all 4 publications cited by Dr Lyons and were not able to find a description of a clinical presentation of a patient with β-tryptase duplication or its effect on serum basal tryptase levels.

We would like to emphasize that our study does not rule out HαT as a modifier of the severity of allergic or anaphylactic responses. Indeed, the study by Greiner et al that is cited in Dr Lyons’ letter does not describe a phenotypic impact of HαT per se in otherwise healthy individuals but instead describes amplification of a known risk (mast cell mediator symptoms or anaphylaxis) conferred by mastocytosis in this population. It is also possible that HαT may be a confounder of other phenotypes such as IgE-mediated allergies; however, it is quite clear that HαT does not impart a pathogenic phenotype by itself as a mono- or oligogenic autosomal dominant disorder. We would recommend caution before attributing a common genetic variant that may be present in up to 23 million individuals in the United States as a cause for a multisystem “disorder,” as the data supporting this notion are simply not confirmed. Doing so without reproducible data in larger cohorts would be fraught with the danger of leaving other underlying causes of the symptoms unaddressed and lead to delays in patient diagnosis and proper treatment.

We wish to thank Dr Lili Zhao, a research associate professor in the Department of Biostatistics, University of Michigan School of Public Health, for helpful discussions regarding the statistical points in this letter.

Cem Akin, MD, PhD
Madeleine B. Chollet, MD, PhD
From the Department of Internal Medicine, Division of Allergy and Immunology, University of Michigan, Ann Arbor, Mich. E-mail: cemakin@med.umich.edu.

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