Hereditary alpha tryptasemia is not associated with specific clinical phenotypes

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Background: Hereditary alpha tryptasemia (HαT) is found in approximately 7% of the population. Associations with a variety of clinical symptoms including gastric reflux, joint hypermobility, dysautonomia, flushing and pruritus, and hymenoptera allergy have variably been described in prior reports. However, our understanding of this genetic trait is limited by a paucity of published studies, referral bias, and conflicting findings at clinical presentation.
Objective: The purpose of this study was to assess the clinical phenotype of HαT in a random biorepository population and in patients with and without mastocytosis referred to the allergy clinic.
Methods: Tryptase copy number allele was assessed using digital droplet PCR. Participants with or without HαT were interviewed and examined by a clinician and surveyed regarding their medical history and symptomology.
Results: HαT was identified in 7.5% of the random biorepository samples and in 18% of patients with mastocytosis. There was no difference in the clinical symptomology or medical history of individuals with HαT compared to controls. Average baseline serum tryptase was higher in individuals with HαT compared to controls, but there was no difference in urinary mast cell activation products.
Conclusions: Elevated baseline serum tryptase was the only consistent phenotypic marker for HαT in this study. There was a higher frequency of HαT in patients with mastocytosis than in the general population. (J Allergy Clin Immunol 2022;149:728-35.)

Key words: *Hereditary alpha tryptasemia, mastocytosis*

Abbreviations used
BST: Baseline serum tryptase
EDS: Ehlers-Danlos syndrome
HαT: Hereditary alpha tryptasemia
IBS: Irritable bowel syndrome
MCAS: Monoclonal mast cell activation syndrome
MGI: Michigan Genomics Initiative

TPSAB1, along with *TPSAB2,* encodes for serum tryptase.[1] *TPSAB1* contains the α allele, the β1 allele, or a combination. *TPSAB2* harbors the β2 and β3 alleles. At baseline, the total number of alpha tryptase and beta tryptase alleles is 4. Hereditary alpha tryptasemia (HαT) is an autosomal-dominant genetic trait that is defined by 1 or more extra copies of the α-tryptase allele in the *TPSAB1* locus.[2] It is found in approximately 5% to 8% of the general population.[2,3] The majority of individuals have a duplication of α-tryptase, but triplication, quadruplication, and quintuplication have been reported.[4] HαT is associated with an elevated baseline serum tryptase (BST) level. Most patients have BST levels greater than 8 ng/mL; Lyons et al[2] found a median BST of 15.9 ng/mL.

A variety of clinical conditions have been attributed to HαT.[5-7] Lyons et al[2] evaluated subjects from 35 families with elevated BST and reported a high prevalence of irritable bowel syndrome (IBS), gastric reflux, joint hypermobility, congenital skeletal abnormalities, retained primary teeth, dysautonomia, chronic arthralgia, recurrent cutaneous flushing and pruritus, sleep disturbance, and Hymenoptera allergy. They also reported 9 individuals with HαT identified in a biorepository to be more likely than controls to experience recurrent cutaneous flushing, Hymenoptera allergy, IBS, retained primary teeth, and dysautonomia. When the results from the 2 analyses were compared, conditions that were significant in both were limited to Hymenoptera allergy, retained primary teeth, and recurrent cutaneous flushing and pruritus. This study was limited in 3 ways that may have played a role in the discrepant clinical findings. First was referral bias. Second, the samples included multiple individuals from the same family who would have had an opportunity to discuss and compare their clinical symptoms before the study. Third, the biorepository sample only included 9 patients with HαT.

Robey et al[3] also examined prevalence and clinical conditions associated with HαT in a UK population. They found that 5% of 423 individuals from an unselected birth cohort had this trait. Clinical features in this random cohort were not available. HαT was similarly found in 5% of a population of patients referred to the allergy clinic for suspected mast cell and allergic disorders, which argues against this trait conferring a higher susceptibility for developing allergic disease. Analysis of 77 patients with HαT in this group showed a high incidence of urticaria/angioedema, skin flushing, abdominal pain, loose stools, and brain fog. In contrast to the findings reported by Lyons et al,[2] joint hypermobility or dysautonomic symptoms were not more

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common in this population, and there was no correlation between α-tryptase allele burden and clinical symptoms. A more recent study reported that anaphylaxis, gastrointestinal, and cutaneous symptoms were present in more than 50% of 101 patients referred to an allergy clinic for mast cell activation symptoms, but there was no control population for comparison.[7]

Given the discrepancy of reported phenotypic variations in studies published so far, as well as the inherent referral bias in studies conducted via allergy clinic referrals, we assessed the clinical phenotype of HαT in a prospective study in an unselected population and compared the findings in patients referred to the allergy clinic with and without mastocytosis.

METHODS

Subjects

Informed consent was provided by all patients who participated in this study. This study was approved by the University of Michigan's institutional review board (HUM00159337).

Participants for this study were recruited prospectively from either the allergy and immunology clinic at the University of Michigan or from the Michigan Genomics Initiative (MGI) biorepository. Participants who were recruited from the clinic were either new or returning patients who were referred for evaluation of possible mast cell disorder. All participants had their BST level[8] checked before enrollment. One hundred patients were recruited between November 2019 and July 2020, with 50 having mastocytosis or monoclonal mast cell activation syndrome (MCAS).[9,10] One participant was withdrawn for not completing the study, and 1 participant was excluded because of an inconclusive bone marrow biopsy result but strong clinical suspicion for MCAS.

MGI is a biorepository made up of samples from tens of thousands of patients. Five hundred random DNA samples were initially tested for tryptase copy number. Eighty-four individuals did not have enough DNA for analysis and were excluded. Of the remaining 416 individuals, 31 had 1 or more extra copies of the tryptase gene. We were given contact information by MGI for an age- and sex-matched group of 100 participants in a 1:2 case-to-control ratio from which to recruit participants. Thirty-seven individuals consented to participate, 2 of whom later withdrew.

In order to be included in the study, all participants had to provide a cheek swab for genetic testing to confirm screening findings of α-tryptase genotype, complete a survey, and allow us to review their medical records. Biorepository DNA samples and cheek swabs were analyzed independently; no links were provided to Gene By Gene (Houston, Tex) to connect samples from the same individual. All participants except 1 mastocytosis patient who had previously had genetic testing for HαT were unaware of the results of their genetic testing before completing the survey and clinical interview. Some clinic participants completed a physical examination for an objective assessment consisting of a joint examination to determine their Beighton score and orthostatic blood pressure as defined by Centers for Disease Control and Prevention criteria. Individuals were excluded from the study if they had a memory disorder preventing them from completing the survey, if they were unable to speak English, or if they did not have access to the internet.

Assessment

TPSAB1 and *TPSAB2* copy numbers were evaluated by Gene By Gene using digital droplet PCR from a cheek swab or DNA sample. This assay determines α and β copy number by comparing it to highly conserved reference sequence *AP3B1* and, if necessary, a secondary reference gene *TERT*. Tryptase, 11beta-prostaglandin F2, prostaglandin D_2, *N*-methylhistamine, and leukotriene E4 values were extracted from the medical record. For any test with multiple values, the average was taken. Clearly identified postanaphylaxis tryptase measurements were excluded from baseline tryptase level calculations. All recruitment, interviews, and chart review were completed by a single investigator. Lists of patients' medical problems and medications were compiled from the medical record and then confirmed with the patients. Patients filled out a survey online based on that published by Lyons et al,[2] which asked about symptomology and included the COMPASS 31 diagnostic criteria for dysautonomia[11] as well as the ROME IV criteria for IBS.[12]

Hymenoptera allergy was assessed in 2 different ways. All study participants were asked to self-report a history of Hymenoptera allergy, including their symptoms. Patients were classified on the basis of their symptoms as either having a large local reaction or anaphylaxis. Because patient self-report may be subject to recall errors, we also completed a chart review on all clinic patients to determine their allergists' assessments regarding possible Hymenoptera allergy. Ehlers-Danlos syndrome (EDS) was also assessed in 2 different ways. All patients were asked whether they had a history of EDS. Clinic patients who completed the physical examination were assessed objectively for hypermobile EDS using the Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome checklist provided by the International Consortium on Ehlers-Danlos Syndromes.

Statistical analysis

Categorical variables were analyzed by the Fisher exact test, while continuous variables were assessed by either unpaired *t* test or Mann-Whitney *U* test if the distribution was not normal. For all analyses, 2-tailed tests were used to assess for significance, and significance was considered a *P* value of less than .05.

RESULTS

Validity of survey

In order to verify the validity of the survey, we compared the survey results of patients with mastocytosis without HαT to those from the biorepository controls. The survey accurately identified symptoms that are classically associated with mastocytosis. Patients with mastocytosis without HαT (n = 40) were significantly more likely than controls from the biorepository (n = 24) to report flushing (53% vs 4%, Fisher exact test .0001, $P < .05$), itching (63% vs 4%, Fisher exact test <.00001, $P < .05$), orthostatic intolerance (40% vs 13%, Fisher exact test .025, $P < .05$), and unexplained symptoms (55% vs 8%, Fisher exact test .0002, $P < .05$). Similarly, patients with mastocytosis and HαT (n = 9) were more likely than biorepository patients with HαT (n = 10) to report flushing (67% vs 0, Fisher exact test .0031, $P < .05$).

Analysis of unselected population

We assessed tryptase copy number in 416 random DNA samples from the biorepository (Table I). Thirty-one individuals (7.5%) had at least 1 extra tryptase copy. Most (n = 27, 87%) had 1 extra α-tryptase allele. One had a unique genotype where there were 4 α-tryptase alleles but only 1 β-tryptase allele, suggesting that 1 β-tryptase allele was lost.

Thirty-five individuals consented to participate in the full clinical study. Eleven people (31.4%) had 1 extra tryptase allele (Table I). One participant had a possible extra β-tryptase allele rather than an extra α-tryptase allele and was removed from subsequent analyses because it is unknown whether this novel mutation has a different phenotype. Demographics of participants with HαT (n = 10) were similar to that of controls (n = 24) (Table II).

There was no statistically significant difference between participants with HαT and controls in the prevalence of asthma, rhinitis, postural orthostatic tachycardia syndrome, EDS, hypothyroidism, anxiety and/or depression, or migraines (Fisher exact test, $P > .05$) (Table III). Patients with HαT and controls reported a similar prevalence of venom allergy, retained primary teeth,

TABLE I. Distribution of alpha and beta tryptase alleles

Sample	No. of extra tryptase alleles	No. of α-tryptase alleles/no. of β-tryptase alleles	N	Mastocytosis classification
Screening biorepository patients	3	5/2	1	
	2	4/2	1	
	1	4/1	1	
	1	3/2	15	
	1	2/3	11	
	1	1/4*	2	
	0	2/2	91	
	0	1/3	188	
	0	0/4	104	
	0	0/3	2	
Biorepository patients who participated in full clinical study	1	4/1	1	
	1	3/2	4	
	1	2/3	5	
	1	1/4*	1	
	0	2/2	1	
	0	1/3	18	
	0	0/4	5	
Clinic patients without mastocytosis or MCAS	3	5/2	1	
	2	3/3	1	
	1	3/2	8	
	1	2/3	9	
	2	2/4*	1	
	0	2/2	5	
	0	1/3	14	
	0	0/4	10	
Clinic patients with mastocytosis or MCAS	2	4/2	2	1 ISM, 1 MIS
	1	3/2	3	2 ISM, 1 ASM
	1	2/3	4	3 ISM, 1 SSM
	0	2/2	12	6 ISM, 1 CM, 1 SSM, 1 MCAS, 3 MIS
	0	1/3	20	14 ISM, 2 CM, 1 SM-AHN, 3 MIS
	0	0/4	8	5 ISM, 2 SSM, 1 SM-AHN

Mastocytosis classification was based on World Health Organization criteria.[10,11]
ASM, Aggressive systemic mastocytosis; *CM*, cutaneous mastocytosis; *ISM*, indolent systemic mastocytosis; *MIS*, mastocytosis in skin; *SM-AHN*, systemic mastocytosis with associated hematologic neoplasm; *SSM*, smoldering systemic mastocytosis.
*Individuals with a possible extra β-tryptase were removed from subsequent analyses.

TABLE II. Demographic data

Sample	Classification	N	Age (years), average (range)	Female, no. (%)
Biorepository	HαT	10	61 (44-73)	5 (50)
	Control	24	62 (30-81)	14 (58)
Clinic, no mastocytosis	HαT	19	45 (24-75)	18 (95)
	Control	29	50 (20-76)	20 (69)
Clinic, mastocytosis	HαT	9	48 (27-73)	7 (78)
	Control	40	52 (23-75)	31 (78)

flushing, itching, sleep disruption, orthostasis, skeletal deformity, IBS, and joint hypermobility. There was no difference in average total autonomic dysfunction score as measured by COMPASS 31 ($t(32) = -0.77$, $P = .45$).

Analysis of allergy clinic patients without mastocytosis or monoclonal mast cell disease

Twenty (41%) of 49 clinic patients without mastocytosis or MCAS had 1 or more extra tryptase alleles (Table I). Most (n = 17, 85%) had 1 extra α-tryptase allele. One had 2 α-tryptase alleles and 4 β-tryptase alleles, suggesting a possible extra β-tryptase allele; data from this participant was removed from subsequent analyses. Demographics for individuals with HαT were similar to controls (Table II).

We compared laboratory markers for mast cell activation between individuals with HαT and controls when available. Many patients did not have urinary markers, and some patients had urinary markers reported as "normal" or less than a particular reference value. We included both an average value and a count of the number of individuals with a positive result (that is, above the upper limit of normal) within each group (Table IV). The average BST was higher for individuals with HαT (mean = 15.8 ng/mL, SD = 4.5) than for controls (mean = 5.3 ng/mL, SD = 3.1)

TABLE III. Selected medical diagnoses and symptoms for patients recruited from biorepository

Characteristic	HαT (n = 10)		Control (n = 24)		*P* value
Medical history					
Asthma	1	10%	3	13%	NS
Rhinitis	4	40%	11	46%	NS
Idiopathic anaphylaxis	0	0	0	0	NS
POTS	0	0	0	0	NS
EDS	0	0	0	0	NS
Hypothyroidism	1	10%	6	25%	NS
Anxiety/depression	3	30%	9	38%	NS
Migraine	1	10%	5	21%	NS
Survey					
MCAS	0	0	0	0	NS
Venom allergy	1	10%	4	17%	NS
Large local reaction only	1	10%	2	8%	NS
Anaphylaxis	0	0	2	8%	NS
Prescribed epinephrine	0	0	1	4%	NS
Retained primary teeth	1	10%	1	4%	NS
Positive tilt table	0	0	0	0	NS
Flushing	0	0	1	4%	NS
Itching	1	10%	1	4%	NS
Gastric reflux	4	40%	5	21%	NS
Chronic pain	7	70%	12	50%	NS
Joint	6	60%	9	38%	NS
Muscle	1	10%	7	29%	NS
Whole body	2	20%	1	4%	NS
Headache	1	10%	4	17%	NS
Sleep disruption	4	40%	11	46%	NS
Orthostasis	0	0	3	13%	NS
Skeletal deformity	0	0	0	0	NS
IBS, self-reported	2	20%	5	21%	NS
IBS, ROME IV	2	20%	1	4%	NS
Joint hypermobility	1	10%	2	8%	NS
COMPASS 31 score (average)	14		18		NS
Orthostatic intolerance	3		6		
Vasomotor	0		1		
Secretomotor	1		2		
Gastrointestinal	6		6		
Bladder	1		1		
Pupillomotor	1		1		
Unexplained symptoms	2	20%	2	8%	NS
Family with unexplained symptoms	1	10%	0	0	NS

EDS, Ehlers-Danlos syndrome; *NS*, not significant ($P > .05$); *POTS*, postural orthostatic tachycardia syndrome.

TABLE IV. Summary of laboratory markers for mast cell activation for patients with HαT and controls

Characteristic	HαT		Control		*P* value
Tryptase					
Average	15.8	n = 19	5.3	n = 29	< .00001
Range	8.1-26.7		2.5-14.3		—
23BPG					
Average	2795	n = 7	2629	n = 14	NS
Elevated marker	2/8	25%	3/15	20%	NS
NMH					
Average	161	n = 10	161	n = 15	NS
Elevated marker	4/10	40%	3/15	20%	NS
LTE_4					
Average	115	n = 7	187	n = 10	NS
Elevated marker	4/8	50%	6/15	40%	NS
One or more elevated urinary marker	7/11	64%	9/17	53%	NS

Data are presented as both averages and as proportion of individuals with elevated urinary marker. Cutoff value for 23BPG was defined as >3263 pg/mg; for NMH, >200 μg/g; and for LTE_4, >104 pg/mg. Total sample size is indicated as denominator of each proportion.
23BPG, 2,3-Dinor-11beta-prostaglandin F2 alpha; *LTE_4*, leukotriene E4; *NMH*, *N*-methylhistamine; *NS*, not significant ($P > .05$).

($t(29) = 9.53$, $P < .00001$). Eighteen (95%) of 19 individuals with HαT had an average tryptase level of ≥11.0 ng/mL. One individual with HαT had a tryptase level of 8.1 ng/mL. The average BST for controls ranged from 2.5 to 14.3 ng/mL. Because the average tryptase for HαT patients is approximately 3 times that of controls, we could roughly calculate a normalized tryptase using the following formula: normalized tryptase = [tryptase/(3 × no. of extra α-tryptase copies)].

Bone marrow biopsy samples were available to review in 11 patients with HαT and 5 controls. None had evidence of clonal mast cell disease, including the 2 controls with the highest BST, at 14.3 and 12.0 ng/mL, respectively. D816V mutation was checked in 8 patients with HαT and 4 controls, and all were negative. One patient with HαT and 1 control had bone marrow biopsy samples that were not available for review but were reportedly normal.

There was no difference in the average urinary level of 2,3-dinor-11beta-prostaglandin F2 alpha between individuals with HαT and controls ($t(19) = 0.33$, $P = .74$) or in the proportion of individuals with elevated urinary 2,3-dinor-11beta-prostaglandin F2 alpha (Fisher exact test 1, $P > .05$). Similarly, there was no difference in the average urinary level of *N*-methylhistamine ($t(22) = -0.01$, $P = .99$) or the proportion of individuals with elevated *N*-methylhistamine (Fisher exact test .38, $P > .05$). The average urinary leukotriene E4 level did not differ between the 2 groups ($t(15) = -0.96$, $P = .35$); nor did the proportion of individuals with an elevated urinary leukotriene E4 level (Fisher exact test .38, $P > .05$).

There was no significant difference in the prevalence of assessed comorbidities or symptoms between these 2 groups (Table V). There was no difference in the prevalence of venom allergy as determined by an allergist. Of note, the number of patients meeting clinical criteria for venom allergy was lower than the number with a self-reported venom allergy. There was no difference in Beighton score or orthostatic hypotension. The average total COMPASS 31 score for dysautonomia did not differ significantly between patients with HαT and controls ($t(46) = -0.9$, $P = .38$).

Combined analysis of biorepository and clinic patients without mastocytosis

When we combined the samples from the biorepository and the allergy clinic to increase the overall sample size (n = 82, comprising 29 with HαT and 53 controls), the results remained the same, with no significant differences in the assessed comorbidities or symptoms (see Table E1 in this article's Online Repository at www.jacionline.org).

Analysis of allergy clinic participants with mastocytosis or monoclonal mast cell disease

Nine (18%) of the patients with mastocytosis or MCAS had 1 or more extra tryptase allele (Table I). The majority of the individuals with HαT (n = 6, 67%) and without HαT (n = 25, 63%) had indolent systemic mastocytosis. Age and sex were similar between patients with mastocytosis or MCAS with HαT and those without HαT (Table II).

The median BST for patients with mastocytosis and HαT (88.8 ng/mL) was higher than the that for patients with mastocytosis without HαT (33.0 ng/mL) ($U = 99$, $P = .04$). When only patients with indolent systemic mastocytosis were assessed, there was no significant difference ($U = 64$, $P = .60$) in the median baseline tryptase for patients with mastocytosis and HαT (n = 6, median = 60.8 ng/mL) and patients with mastocytosis without HαT (n = 25, median = 40 ng/mL).

There was no significant difference in the prevalence of comorbidities or reported symptoms between patients with mastocytosis and HαT and those without HαT (Table VI). There was no difference in the prevalence of venom allergy as determined by an allergist or in self-reported history of venom allergy (Fisher exact test, $P > .05$). The average total COMPASS 31 score for dysautonomia did not differ significantly between patients with HαT and controls ($t(47) = -0.68$, $P = .50$).

Identification of possible β-tryptase duplications

Three patients—1 from the clinic and 2 from the biorepository—were identified as having a possible extra β-tryptase allele (see the case report in this article's Online Repository at www.jacionline.org). The clinic patient had 4 copies of the β-tryptase allele and 2 copies of the α-tryptase allele, which suggests that he had at least 1 extra β-tryptase allele and either a second extra β-tryptase allele or an extra α-tryptase allele. His history was only notable for diffuse hives without anaphylaxis after a Hymenoptera sting, retained primary teeth, and an elevated tryptase of 16.6 ng/mL. Both biorepository patients had 1 α- and 4 β-tryptase alleles on genetic testing, suggesting that they each have 1 extra copy of the β-tryptase allele. Only 1 biorepository patient consented to participate in the survey but was unremarkable.

DISCUSSION

The purpose of this study was to examine the medical conditions and symptoms associated with HαT. To date, only a handful of studies have been published on this topic. In our study, HαT was found in 7.5% of individuals from the biorepository, which is consistent with previous studies.[2,3] There was an overlap in BST for controls and individuals with HαT between 8 and 14 ng/mL. Unlike Lyons et al,[2] our study did not find any particular clinical features to be associated with HαT using similar survey questions. We also did not find an association between postural orthostatic tachycardia syndrome or hypermobile EDS and HαT. There was no difference in urinary markers for mast cell activation between patients with HαT and controls. This is consistent with findings reported by Lyons et al that mast cells grown from patients with HαT did not have a hyperactive phenotype.[2] While cutaneous and gastrointestinal symptoms were common in clinic patients with HαT, they had a similar frequency in those without HαT.

We did find an association between mastocytosis and HαT, with 18% of the mastocytosis patients enrolled onto this study having both mastocytosis and HαT. These results are similar to the findings of Greiner et al,[13] who reported the frequency of HαT to be 17.2% in their mastocytosis population. They also reported more venom allergy and severe cardiovascular symptoms in their mastocytosis population with HαT compared to those without HαT. While the frequency of venom allergy was also higher in our population with HαT, this did not reach statistical significance, which may be due to sample size. Our study was not designed to evaluate differences in the severity of mastocytosis or allergic conditions in patients with HαT; however, because other studies[13,14] have reported that HαT may serve as a biomarker for more severe disease, additional research is needed

TABLE V. Selected medical diagnoses, symptoms, and physical examination findings for patients referred to clinic for evaluation of mast cell disorder without clonal mast cell disorder

Characteristic	HαT		Control		*P* value
Medical history	**N = 19**		**N = 29**		
Asthma	3	16%	10	34%	NS
Rhinitis	11	58%	21	72%	NS
Idiopathic anaphylaxis	2	11%	2	7%	NS
POTS	6	32%	7	24%	NS
EDS	4	21%	11	38%	NS
Hypothyroidism	5	26%	5	17%	NS
Anxiety/depression	9	47%	12	41%	NS
Migraine	8	42%	5	17%	NS
Chart review	**N = 19**		**N = 25**		
Venom allergy diagnosis by allergist	2	11%	3	12%	NS
Physical examination	n = 17		n = 21		
Positive Beighton score	3	18%	6	29%	NS
Hypermobile EDS	2	12%	6	29%	NS
Orthostatic hypotension	4	24%	5	24%	NS
Survey	**N = 19**		**N = 29**		
MCAS	10	53%	19	66%	NS
Venom allergy	4	21%	13	45%	NS
Large local reaction only	1	5%	5	17%	NS
Anaphylaxis	3	16%	8	28%	NS
Prescribed epinephrine	3	16%	6	21%	NS
Retained primary teeth	5	26%	7	24%	NS
Positive tilt table	4	21%	6	21%	NS
Flushing	13	68%	23	79%	NS
Itching	12	63%	19	66%	NS
Gastric reflux	3	16%	10	34%	NS
Chronic pain	12	63%	22	76%	NS
Joint	11	58%	16	55%	NS
Muscle	9	47%	15	52%	NS
Whole body	6	32%	11	38%	NS
Headache	9	47%	13	45%	NS
Sleep disruption	18	95%	27	93%	NS
Orthostasis	11	58%	22	76%	NS
Skeletal deformity	2	11%	1	3%	NS
IBS, self-reported	12	63%	14	48%	NS
IBS, ROME IV	6	32%	9	31%	NS
Joint hypermobility	7	37%	17	59%	NS
COMPASS 31 score (average)	36		42		NS
Orthostatic intolerance	15		18		
Vasomotor	1		2		
Secretomotor	5		7		
Gastrointestinal	10		11		
Bladder	2		2		
Pupillomotor	2		3		
Unexplained symptoms	2	20%	2	8%	NS
Family with unexplained symptoms	1	10%	0	0	NS

EDS, Ehlers-Danlos syndrome; *NS*, not significant ($P > .05$); *POTS*, postural orthostatic tachycardia syndrome.

to determine if HαT should be routinely tested for in clinical practice. In addition, future studies may include analysis of response to inducible mast cell degranulation such as vibration and exercise between individuals with or without HαT.

Similar to Greiner et al,[13] our study also found a higher median BST in patients with HαT and mastocytosis compared to patients with mastocytosis without HαT when all subtypes of mastocytosis are included in the analysis; however, the finding that the median BST is similar in patients with indolent systemic mastocytosis with and without HαT suggests that differences in tryptase level between groups may be driven by an unequal distribution of different subtypes of mastocytosis as well as by HαT.

To our knowledge, this study is the first to report 3 patients with possible β-tryptase duplications identified by digital droplet PCR. We were unable to verify these possible β-tryptase duplications by using other laboratory techniques or by testing additional family members for this mutation. Additional studies to verify β-tryptase duplications are indicated. Two of 416 unselected biorepository samples had a possible β duplication, which suggests that this mutation is present in approximately 0.5% of the population. The presence of possible β-tryptase duplications in our sample calls into question HαT as a unified diagnosis in individuals identified to have tryptase gene copy number variations, and whether "hereditary tryptasemia"

TABLE VI. Selected medical diagnoses and symptoms for patients with mastocytosis or MCAS

Characteristic	HαT + mastocytosis		Mastocytosis without HαT		*P* value
Medical history	**N = 9**		**N = 40**		
Asthma	2	22%	1	3%	NS
Rhinitis	6	67%	19	48%	NS
POTS	0	0	1	3%	NS
EDS	0	0	0	0	NS
Hypothyroidism	1	11%	11	28%	NS
Anxiety/depression	3	33%	16	40%	NS
Migraine	0	0	3	8%	NS
Chart review	**N = 9**		**N = 38**		
Venom allergy diagnosis by allergist	1	11%	3	8%	NS
Physical examination	**N = 3**		**N = 17**		
Positive Beighton score	0	0	0	0	NS
Hypermobile EDS	0	0	0	0	NS
Orthostatic hypotension	1	33%	3	18%	NS
Survey	**N = 9**		**N = 40**		
Venom allergy	2	22%	3	8%	NS
Large local reaction only	1	11%	0	0	NS
Anaphylaxis	1	11%	3	8%	NS
Prescribed epinephrine	2	22%	3	8%	NS
Retained primary teeth	0	0	5	13%	NS
Positive tilt table	0	0	1	3%	NS
Flushing	6	67%	21	53%	NS
Itching	2	22%	25	63%	NS
Gastric reflux	2	22%	18	45%	NS
Chronic pain	5	56%	18	45%	NS
Joint	4	44%	13	33%	NS
Muscle	3	33%	9	23%	NS
Whole body	2	22%	6	15%	NS
Headache	2	22%	5	13%	NS
Sleep disruption	7	78%	24	60%	NS
Orthostasis	4	44%	16	40%	NS
Skeletal deformity	0	0	0	0	NS
IBS, self-reported	1	11%	15	38%	NS
IBS, ROME IV	2	22%	5	13%	NS
Joint hypermobility	1	11%	3	8%	NS
COMPASS 31 score (average)	23		27		NS
Orthostatic intolerance	9		11		
Vasomotor	1		1		
Secretomotor	3		4		
Gastrointestinal	8		8		
Bladder	0		1		
Pupillomotor	2		3		
Unexplained symptoms	5	56%	22	55%	NS
Family with unexplained symptoms	3	33%	4	10%	NS

EDS, Ehlers-Danlos syndrome; *NS*, not significant ($P > .05$); *POTS*, postural orthostatic tachycardia syndrome.

may be a more inclusive term to use when referring to the diagnosis of such patients.

The strengths of this study are that it included both individuals with HαT and age- and sex-matched controls and that these participants were identified from a variety of different populations with one sample from an unbiased biorepository (the largest unselected population reported so far), a second sample from an allergy clinic using referrals for patients with either an elevated tryptase level or suspicion of mast cell disease, and a third sample of patients with mastocytosis. This variety is important so that we might account for variabilities in symptoms and physical findings that may be affected by age and sex, such as joint flexibility. In addition, findings such as orthostatic hypotension and joint flexibility were assessed by physical examination, and the venom allergy history was verified in allergy records when available. While the survey was able to pick up symptoms classically associated with mastocytosis relative to healthy controls, no differences were found in symptoms or medical conditions between controls and individuals with HαT. This may suggest that previous reports attributing phenotypic findings to HαT may be subject to referral bias because those with unexplained symptoms, anaphylaxis, postural orthostatic tachycardia syndrome, and EDS may be more likely to be checked for tryptase levels, which would affect the referral population's characteristics. Considering that this genetic variant is common, being found in 7.5% of the population, this is not surprising. While some patients with HαT may have symptoms related to this genetic variant, it does not appear to be uniform or pervasive. An elevated BST was the only consistent marker for HαT.

The findings in this study also suggest that HαT by itself cannot be classified as a mast cell activation disorder, consistent with the conclusions reached by Robey et al,[3] although it does not exclude the possibility that it may modify or enhance the severity of certain symptoms such as IgE-mediated venom allergies, especially in patients with mastocytosis. The primary limitation of this study was its sample size. This study did not contain enough individuals with more than 1 extra α-tryptase allele to assess for the discrepancy reported in previous studies.[2,3] Another limitation of this study is that venom allergy was self-reported, with skin and/or serum testing only undertaken for clinic patients with a clinical history of venom allergy. Future research expanding on this study would help verify our results as they differ from previous studies.

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Clinical implications: Patients with hereditary alpha tryptasemia (HαT) have elevated baseline serum tryptase but do not reliably exhibit a certain set of clinical features. HαT occurs more frequently in patients with mastocytosis.

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CASE REPORT OF POSSIBLE β-TRYPTASE DUPLICATION

Clinic patient

The patient was a 66-year-old man referred to the allergy clinic for evaluation of a venom allergy. He had a history of diffuse hives without anaphylaxis after a Hymenoptera sting and was found to have an elevated tryptase of 16.6 ng/mL. He also had a history of allergic rhinitis, asthma, chronic obstructive pulmonary disease, steatohepatitis, osteoarthritis, benign prostatic hypertrophy, and pseudogout. Genetic testing revealed 4 copies of the β-tryptase allele and 2 copies of the α-tryptase allele. This result suggested that he had at least 1 extra β-tryptase allele and either a second extra β-tryptase allele or an extra α-tryptase allele. His survey results were largely unremarkable. He denied a personal history of Ehlers-Danlos syndrome, postural orthostatic tachycardia syndrome, or a family history of mastocytosis. He reported a history of retained primary teeth but denied a history of itching, flushing, dysphagia, chronic pain, dysautonomia, sleep disturbance, or skeletal deformity. His COMPASS 31 score was 13 of 100. At physical examination, he had a Beighton score of 0, and he did not have orthostatic hypotension.

Biorepository patients

Both biorepository patients had 1 α- and 4 β-tryptase alleles on genetic testing, suggesting that they each had 1 extra copy of the β-tryptase allele. Only 1 biorepository patient consented to participate in the survey. This patient was a 79-year-old man with a history of atrial fibrillation, hypertension, hypothyroidism, and hyperlipidemia. He denied a personal history of venom allergy, Ehlers-Danlos syndrome, postural orthostatic tachycardia syndrome, or a family history of mastocytosis. He denied a history of itching, flushing, dysphagia, retained primary teeth, chronic pain, dysautonomia, sleep disturbance, or skeletal deformity. His COMPASS 31 score was 15 of 100.

TABLE E1. Combined analysis of patients with or without HαT for individuals recruited from MGI and the allergy clinic without mastocytosis or MCAS

Characteristic	HαT (n = 29)		Control (n = 53)		*P* value
Medical history					
Asthma	4	14%	13	25%	NS
Rhinitis	15	52%	32	60%	NS
Idiopathic anaphylaxis	2	7%	2	4%	NS
POTS	6	21%	7	13%	NS
EDS	4	14%	11	21%	NS
Hypothyroidism	6	21%	11	21%	NS
Anxiety/depression	12	41%	21	40%	NS
Migraine	9	31%	10	19%	NS
Survey					
MCAS	10	34%	19	36%	NS
Venom allergy	5	17%	17	32%	NS
Large local reaction only	2	7%	7	13%	NS
Anaphylaxis	3	10%	10	19%	NS
Prescribed epinephrine	3	10%	7	13%	NS
Retained primary teeth	6	21%	8	15%	NS
Positive tilt table	4	14%	6	11%	NS
Flushing	13	45%	24	45%	NS
Itching	13	45%	20	38%	NS
Gastric reflux	7	24%	15	28%	NS
Chronic pain	19	66%	34	64%	NS
Joint	17	59%	25	47%	NS
Muscle	10	34%	22	42%	NS
Whole body	8	28%	12	23%	NS
Headache	10	34%	17	32%	NS
Sleep disruption	22	76%	38	72%	NS
Orthostasis	11	38%	25	47%	NS
Skeletal deformity	2	7%	1	2%	NS
IBS, self-reported	14	48%	19	36%	NS
IBS, ROME IV	8	28%	10	19%	NS
Joint hypermobility	8	28%	19	36%	NS
COMPASS 31 score (average)	29		53		NS
Orthostatic intolerance	11		13		
Vasomotor	1		1		
Secretomotor	4		5		
Gastrointestinal	9		9		
Bladder	2		1		
Pupillomotor	2		2		
Unexplained symptoms	18	62%	21	40%	NS
Family with unexplained symptoms	6	21%	10	19%	NS

EDS, Ehlers-Danlos syndrome; *NS*, not significant ($P > .05$); *POTS*, postural orthostatic tachycardia syndrome.