



Hereditary Alpha-Tryptasemia: a Commonly Inherited Modifier of Anaphylaxis

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Abstract

Purpose of Review Hereditary alpha-tryptasemia (H α T) is an autosomal dominant genetic trait and a common cause of elevated basal serum tryptase in Western populations. It is a risk factor for severe anaphylaxis among individuals with venom allergy and an established modifier of anaphylaxis and mast cell mediator-associated symptoms among patients with systemic mastocytosis. Understanding the physiology of tryptases and how this may relate to the clinical features associated with H α T is the first step in identifying optimal medical management and targets for novel therapeutics.

Recent Findings H α T prevalence is increased in both clonal and non-clonal mast cell-associated disorders where it augments symptoms of immediate hypersensitivity, including anaphylaxis. The unique properties of naturally occurring α/β -tryptase heterotetramers may explain certain elements of phenotypes associated with H α T, though additional mechanisms are being evaluated.

Summary This review provides an overview of the clinical and translational studies that have identified H α T as a modifier of mast cell-associated disorders and anaphylaxis and discusses mechanisms that may potentially explain some of these clinical findings.

Keywords Hereditary alpha-tryptasemia · Basal serum tryptase · Anaphylaxis · Mastocytosis

Introduction

Anaphylaxis is a severe and potentially fatal immediate hypersensitivity reaction that may present with variable clinical symptoms. In keeping with precision medicine concepts, biomarkers in predicting risk and severity of anaphylaxis would be useful in conjunction with proposed new therapies. Although both clonal mast cell diseases and elevated basal serum tryptase (BST) of unknown cause(s) have previously been associated with anaphylaxis severity [1–9], historical studies have not systemically evaluated for other causes of BST elevation such as the recently described autosomal dominant genetic trait

hereditary alpha-tryptasemia (H α T) that is associated with elevated BST. This review provides an overview of the clinical data establishing H α T as the common cause of elevated BST in the general population and as a modifier of anaphylaxis severity and mast cell-associated disorders. We also discuss the clinical role for tryptase genotyping and describe putative mechanisms that may partially explain these clinical findings.

Importance of Distinguishing Acute from Basal Serum Tryptase (BST) Elevations

Tryptase is a protein expressed abundantly by mast cells and, to a much lesser extent, basophils, in healthy individuals [10, 11]. Mature tryptases are tetrameric serine proteases stored in mast cell secretory granules that act as allergic mediators contributing to type 2 inflammation [12]. Pro-tryptases, some of which are converted into mature tetrameric tryptases, are also secreted constitutively into serum in their monomeric forms where these inactive zymogens make up the detectable tryptases in serum of healthy individuals at baseline [13, 14]. In the absence of immediate hypersensitivity reactions, pro-tryptases also comprise the detectable forms of tryptase found

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in the serum of patients with systemic mastocytosis [15, 16]. During mast cell degranulation, such as IgE-mediated immediate hypersensitivity reactions, mature tryptases are released and contribute to symptoms of type I allergic reactions. In this setting, an acute rise that may be observed in serum tryptase is a useful biomarker that can support the clinical diagnosis of anaphylaxis [17].

In contrast to acute rises in serum tryptase, elevated basal serum tryptase (BST) (>11.4 ng/mL) is common and estimated to occur in 4–6% of the general populations in which it has been studied [1, 18]. While some BST elevations may be due to end-stage renal disease or clonal expansion of myeloid or mast cells, including mastocytosis [19–21], recent findings indicate that H α T is the culprit in most individuals in the general population [22–25].

H α T is an autosomal dominant genetic trait caused by increased copies of *TPSAB1* encoding α -tryptase. Near-complete penetrance has been reported among cohorts with H α T where virtually all affected individuals have BST values above 8 ng/mL. At the time of publication of this manuscript, as many as four extra copies of *TPASB1* have been reported in families with H α T and BST levels have been shown to follow a gene-dosage with duplications yielding average BST levels of 15 ± 5 ng/mL, triplications 24 ± 6 ng/mL, and quintuplications 37 ± 14 ng/mL [26] (Table 1).

Interpretation of Tryptase Genotyping by Droplet-Digital PCR

Conventional next-generation sequencing, Sanger sequencing, and microarray technologies cannot accurately identify H α T due to the repetitive nature of the tryptase locus and high sequence homology between paralogous genes. Diagnosis can be made through a droplet-digital PCR-based genotyping assay. The assay detects both α - and β -tryptase sequences at *TPSAB1* and *TPSB2* (the latter of which has only been reported to encode β -tryptase) within the tryptase locus. Wild-type tryptase genotypes therefore contain a total of four

gene copies. Because *TPSAB1* and *TPSB2* are in near-complete linkage disequilibrium encoding sequences at these two loci are linked into two haplotypes—one inherited from each parent—both containing *TPSAB1* and *TPSB2* sequences. Canonical associated genotypes are $\alpha\beta/\alpha\beta$, $\alpha\beta/\beta\beta$, or $\beta\beta/\beta\beta$. Individuals with H α T have an additional α -tryptase on a single allele that would result in an $\alpha\alpha\beta$ allele in the case of a duplication (Table 1). Because the wild-type allele in trans that is inherited from the parent without H α T may either contain two β -tryptase sequences ($\beta\beta$) or one α - and one β -tryptase sequence ($\alpha\beta$), the resulting genotype may be $\alpha\alpha\beta/\beta\beta$, or $\alpha\alpha\beta/\alpha\beta$. A common misconception is that the $\alpha\alpha\beta/\beta\beta$ genotype results from increased β -tryptase, because there are three β -tryptase sequences. While β -tryptase encoding gene copy number variation has been reported and may occur more frequently in certain racial groups, it does not segregate with elevated BST in families. In contrast, elevated BST dominantly inherited in a family—which is the common observation—has universally been identified to associate with an allele carrying a *TPSAB1* gene replication encoding α -tryptase even when additional β -tryptase copies are also found and is thus H α T (Table 1).

Clinical Features Associated with H α T

While data in unselected populations remain limited, the phenotypes associated with H α T reported thus far have been heterogeneous. Moreover, because most reports of individuals with H α T have been from centers that focus on genetic syndromes and/or mast cell-associated disorders, significant referral biases may exist in these populations and data. In the only currently published study to have examined symptoms among unselected adults, approximately one third of otherwise healthy individuals with H α T had minimal complaints, one third had mild to moderate symptoms, and one third reported pervasive multisystem complaints [23]. Of the most common symptoms reported in multiple cohorts, approximately one third to one half of symptomatic individuals

Table 1 Tryptase genotypes and corresponding BST levels

Additional <i>TPSAB1</i> * copy number	0	1	2	3	4
Tryptase genotypes [†]	$\beta, \beta/\beta, \beta;$ $\alpha, \beta/\beta, \beta;$ $\alpha, \beta/\alpha, \beta;$ $\beta, \beta, \beta/\alpha, \beta;$ $\beta, \beta, \beta/\beta, \beta$	$\alpha\alpha, \beta/\beta, \beta;$ $\alpha\alpha, \beta/\alpha, \beta;$ $\alpha\alpha, \beta\beta/\beta, \beta;$ $\alpha\alpha, \beta\beta/\alpha, \beta$	$\alpha\alpha, \beta/\alpha\alpha, \beta;$ $\alpha\alpha\alpha, \beta/\beta, \beta;$ $\alpha\alpha\alpha, \beta/\alpha, \beta$	$\alpha\alpha\alpha, \beta/\alpha\alpha, \beta$	$\alpha\alpha\alpha\alpha, \beta/\beta, \beta;$ $\alpha\alpha\alpha\alpha, \beta/\alpha, \beta$
BST (ng/mL), median (range)	4.1 (0–14.4 [‡])	14.5 (7.5–31.5)	21.7 (14–39.5)	27.3 (23.4–40)	37 (25.5–62.7)

* Gene replications encoding β -tryptases may potentially arise from *TPSAB1* or *TPSB2*. [†] Tryptase genotypes include coding sequences at *TPSAB1* and *TPSB2*. [‡] Elevated BST without increased *TPSAB1* copy number encoding α -tryptase has not been observed to segregate within families and is likely a result of an occult indolent clonal myeloid process

reported irritable bowel syndrome (IBS)-like symptoms and/or cutaneous symptoms such as flushing and pruritus. Angioedema and urticaria were less commonly present. For some individuals, symptoms occurred spontaneously, although vibration or minor trauma were also frequently reported precipitants.

Several other clinical manifestations have been associated with H α T and are currently being studied for generalizability, such as connective tissue abnormalities (e.g., joint hypermobility and retained primary dentition), dysautonomia (e.g., orthostatic hypotension), eosinophilic gastrointestinal disease, food intolerances, other IgE-mediated allergic reactions, and constitutional symptoms, such as chronic pain and fatigue. While studies are ongoing, several of these phenotypes have been associated with elevated BST in unselected and ungenotyped cohorts [1–3, 23, 24, 27].

One of the most salient features of the first cohort described with H α T that has been validated, was an increased prevalence of systemic immediate hypersensitivity reactions [23]; this has since been replicated in yet another study [28•]. Moreover, IgE-mediated immediate hypersensitivity to stinging insects was initially reported to not only affect approximately one fifth of patients recruited with H α T but also one fifth of the small validation cohort of ostensibly healthy adult volunteers subsequently found to have H α T [23].

Elevated BST as a Risk Factor for Anaphylaxis Prevalence and Severity

Acute and basal elevations in serum tryptase are well-established biomarkers that support the clinical diagnoses of anaphylaxis and clonal mast cell disorders, respectively. However, several studies have also identified elevated BST as a biomarker associated with an increased prevalence and severity of anaphylaxis in different contexts. In one such study, cases of all-cause anaphylaxis were more prevalent among patients with elevated BST (>11.4 ng/mL) when compared to those with normal serum levels at baseline (21% vs. 14%); severe reactions (Mueller grade III/IV) [29] occurred most often in subjects with BST >20 ng/mL (BST <11.4 ng/mL: 2.8%; 11.5–20 ng/mL: 5.9%; >20 ng/mL: 12.4%) [9]. In a similar study, BST levels were found to be significantly higher among patients with the most severe anaphylaxis (grade IV: 6.61 ng/mL) as compared to those with more moderate reactions (grades II/III: 4.71 ng/mL) [4].

Multiple studies examining specific anaphylaxis triggers have identified a clear relationship between elevated BST and the severity of allergic reactions to stinging insects, most notably Hymenoptera species, where the prevalence of elevated BST is increased among venom allergic patients experiencing moderate to severe anaphylaxis [2, 30••]. In one such large case-control study in an outpatient clinic setting 24% of

patients with elevated BST were reported to have a significantly associated adverse reaction to insect stings [1]. Another study correlated basal serum tryptase levels to initial allergic reaction severity and found a significant association between a sting challenge reaction and elevated BST [5]. The likelihood of a severe anaphylactic reaction after a field sting has also been shown to increase significantly with higher BST levels [6].

Data correlating BST levels with anaphylaxis severity following exposure to allergens other than venom remain limited. In pediatric food allergic patients, one study of affected children demonstrated a positive correlation between elevated BST and anaphylaxis severity, where cutoff values of 5.7 ng/mL and 14.5 ng/mL were associated with 50% and 90% predictive probabilities of moderate to severe anaphylaxis, respectively [3]. Another study evaluating factors predicting anaphylaxis in children with tree nut allergies noted BST levels were significantly higher in the anaphylactic group compared with the non-anaphylactic group, and BST levels of 1.94 ng/mL and 5.30 ng/mL predicted clinical reactivity probabilities at 50% and 95%, respectively [31]. These results suggest that elevated BST levels may be associated with more severe anaphylaxis in children with food allergy, though in at least one additional study of pediatric food allergy no individuals were identified as having elevated BST [32]. Further studies that include tryptase genotyping are needed to better clarify this potential association.

Other anaphylactic triggers, such as general anesthetic agents, have also been investigated in relation to elevated BST. In one study looking at IgE-mediated hypersensitivity reactions to anesthetic agents, severe reactions were associated with higher levels of basal tryptase [33]. However, these results have not been replicated in other small cohort studies.

Data to suggest that when present, elevated BST may modify anaphylaxis severity more generally exists in studies of patients with reactions resulting from no identifiable trigger, namely idiopathic anaphylaxis. Two unrelated studies have reported elevated BST in 12–17% of individuals with idiopathic anaphylaxis in whom no evidence of clonal mast cell disease could be identified [34, 35].

Two additional retrospective clinical studies reported a history of anaphylaxis in 21–36% of individuals with elevated BST [1, 7]. While these latter studies did not systemically evaluate for mastocytosis, clonal mast cell disease alone is unlikely to explain the findings. The larger of the two studies reported nearly 200 individuals out of approximately 15,000 (1.3%) with BST >11.4 ng/mL; this prevalence is significantly greater than even the highest current estimates for the prevalence of mastocytosis [36].

In aggregate, these studies have demonstrated an association between elevated BST and anaphylaxis prevalence and severity in a variety of contexts. While clonal mast cell disease likely contributes to this association, it does not appear to fully

account for the clinical findings. This phenomenon is provocative but since neither tryptase genotyping nor complete evaluation for clonal disease was undertaken in the majority of these studies, any conclusions have remained speculative. However, a number of recent studies have sought to clarify the basis underlying the clinical association of elevated BST with anaphylaxis prevalence and severity.

HaT is Associated with Severe Hymenoptera Venom-Induced Anaphylaxis

While many individuals with elevated BST and venom allergy have underlying clonal mast disease, only recently have individuals with venom allergy been evaluated for other causes of elevated BST such as H α T. In the only study to examine the effects of H α T in an ostensibly healthy cohort of adults, those who were ultimately identified with H α T were significantly more likely to experience a systemic venom reactions compared to those without H α T (odds ratio 11.4) [23].

In a follow-up study [30••] examining two large cohorts of Hymenoptera-allergic individuals from Italy and Slovenia, H α T was at least twice as common ($\geq 8.5\%$) in Italian individuals with severe (grade IV) Hymenoptera venom-induced anaphylaxis (HVA) compared to the general population. H α T also accounted for 81% (21/26) of those with elevated BST who had no detectable evidence of clonal mast cell disease after work-up that included bone marrow biopsy. More than 14% (3/21) of those screened with systemic mastocytosis and grade IV HVA were also found to have concomitant H α T.

In the Slovenian cohort, H α T was also seen approximately twice as often (9.2%, 21/229) among those with grade IV HVA as compared with individuals with all lesser grades of HVA (4.3%, 12/278). Consistent with the identified association between H α T and systemic mastocytosis among individuals with grade IV HVA in the Italian cohort, all individuals found to have both H α T and evidence of clonal mast cell disease also had grade IV HVA. Interestingly, the overall prevalence of H α T among all Hymenoptera venom allergic individuals in the Slovenian cohort—which is the only referral center in that country for venom allergy—was comparable to that of the general population. This suggests that individuals with H α T are not necessarily more likely to be sensitized or to develop an IgE-mediated allergy to Hymenoptera venom, but instead are more likely to have a severe reaction if they are allergic [23].

Although a major factor contributing to the association between elevated BST and severe Hymenoptera venom allergy is clonal mast cell disease, H α T also contributes to this association. Moreover, these risk factors appear to impart an additive risk of severe HVA. Additional studies of individuals with HaT and HVA will help answer outstanding questions,

including the durability of venom immunotherapy (VIT) in these patients, and whether individuals with HaT and HVA should undergo prolonged or even lifelong VIT as recommended for patients with clonal mast cell disease.

HaT is Associated with Systemic Mastocytosis and Augments Immediate Hypersensitivity Symptoms

Patients with systemic mastocytosis are at increased risk for systemic anaphylaxis relative to the general population [8]. In two different studies, symptomatic individuals with H α T were found to have increased numbers of mast cells in bone marrow with some unique morphologic features compared to healthy volunteers or individuals with mast cell activation syndrome without concomitant H α T [28, 30••]. These findings suggest that this genetic trait may affect mast cell homeostasis [22]. While previous reports had raised the possibility that H α T could be associated with clonal mast cell disease [37], two recent studies have firmly established the association and clinical impact of H α T in systemic mastocytosis [30••, 38••].

In the first study, a cohort of mastocytosis patients at the NIH Clinical Center was genotyped irrespective of BST level, or history of venom allergy or anaphylaxis. Greater than 12% (10/82) of individuals with systemic mastocytosis were found to have concomitant H α T compared to 5.3% (21/398) of non-atopic disease controls identified using whole genome sequence analysis and 5.6% (7/125) of healthy volunteers genotyped using droplet-digital PCR. Of the patients with concomitant H α T and systemic mastocytosis, some lacked the commonly acquired *KIT* p.D816V pathogenic variant and had well-differentiated mast cell infiltrates, suggesting that H α T may predispose individuals to a unique molecular endotype of systemic mastocytosis.

Secondary analysis of clinical phenotypes showed that while 49% (40/82) of the total cohort of systemic mastocytosis patients had a history of anaphylaxis—a relatively increased prevalence relative to reports in the literature [9] potentially due selection bias—90% (9/10) of individuals with systemic mastocytosis and concomitant H α T had a history of anaphylaxis [30••]. These findings were the first to suggest that H α T was associated with an increased risk for anaphylaxis among individuals with systemic mastocytosis.

In a follow-up study of European cohorts, investigators found that 17% of their patients with systemic mastocytosis had concomitant H α T. Among these patients, HaT was associated with an increased prevalence of anaphylaxis, as a gene dosage effect was observed on mast cell mediator-associated symptoms as determined using a validated symptom scoring system. In contrast to the US group's findings, the associations with absent *KIT* p.D816V and well-differentiated mast cell infiltrates were not observed in the European study.

However, the variant allele frequency of *KIT* p.D816V was observed to be significantly lower in systemic mastocytosis patients with H α T, compared to those with systemic mastocytosis alone [38••].

In both studies, the prevalence of systemic anaphylaxis among individuals with systemic mastocytosis and H α T was approximately twice than that observed in patients with systemic mastocytosis alone. The cause for anaphylaxis reported included foods, drugs, Hymenoptera venom, and idiopathic presentations suggesting that modification of anaphylaxis in systemic mastocytosis was not related to a particular exposure or agent. However, Hymenoptera reactions were more frequently associated with H α T in systemic mastocytosis patients from the European study.

One theory for the increased prevalence of H α T among individuals with systemic mastocytosis is that the disease-associated clinical phenotypes, such as anaphylaxis, are augmented by H α T, increasing the likelihood of affected patients seeking medical attention. An alternative, non-mutually exclusive theory posits that α -tryptase expression may lead to altered mast cell proliferation or homeostasis resulting from an unclear mechanism. Additional mechanistic and clinical studies are needed to evaluate the validity of these two theories.

The clinical utility of tryptase genotyping may prove to be useful when considering a bone marrow biopsy, as clonal mast cell disease was identified in all individuals with an elevated BST and wild-type *TPSAB1* copy number within NIH cohorts. Additionally, for those individuals with an elevated BST without concerning features reported in clonal mast cell disease patients, deferring an invasive procedure may be reasonable if an alternative explanation, such as H α T or significant renal impairment, is present.

H α T is Associated with Severe Idiopathic Anaphylaxis

Four separate studies have found an association between elevated BST and an increased risk of developing idiopathic anaphylaxis in patients with both clonal and non-clonal mast cell disorders. However, none of these evaluated patients for the presence of both clonal disease and H α T [1, 7, 34, 35]. In order to determine the potential effect of H α T on severe idiopathic anaphylaxis among individuals without clonal mast cell disease, a cohort of individuals with idiopathic anaphylaxis at the NIH Clinical Center underwent tryptase genotyping and an extensive evaluation for the presence of concomitant clonal mast cell disease. A full 17% (8/47) of the cohort had H α T and 2/4 individuals with evidence of clonal mast cell disease that did not meet WHO criteria for the diagnosis of systemic mastocytosis also had H α T [20]. Even after excluding those with clonal disease not meeting criteria for systemic mastocytosis, a significant association between idiopathic

anaphylaxis and H α T was observed (odds ratio = 2.9). Importantly, H α T accounted for elevated BST levels in all individuals with idiopathic anaphylaxis without evidence of clonal mast cell disease. These data suggest that H α T increases the risk for severe anaphylaxis independent of concomitant clonal mast cell disease and antigenic trigger though additional cohort studies need to be conducted.

Tryptase Heterotetramers May Contribute to Immediate Hypersensitivity Symptoms

Mechanisms explaining the association of increased α -tryptase encoding *TPSAB1* gene copy, resulting in α -tryptase over-expression, and severe immediate hypersensitivity symptoms are unproven. However, identification of spontaneously forming α/β -tryptase heterotetramers in mast cells, and likely basophils, has provided insight into at least two possible contributing mechanisms (Fig. 1).

Mature human tryptases are neutral serine proteases that are pre-formed in mast cells where they are the most abundant protein stored in secretory granules [39, 40]. Following mast cell activation, degranulation and acute release of tryptases and other mediators contribute to the symptoms of immediate hypersensitivity reactions and, in severe cases, anaphylaxis. To form mature tryptase enzyme, pro-tryptase zymogens must undergo step-wise proteolytic processing in order to form tetramers stabilized by heparin [41]. α -Tryptase homotetramers lack detectable in vitro enzymatic activity, whereas β -tryptase homotetramers have trypsin-like serine proteinase activity [8]. Recently described α/β -tryptase heterotetramers exhibit enhanced stability and have unique properties that may potentially contribute to clinical findings [42••].

At concentrations believed to mimic physiologic conditions, α/β -tryptase heterotetramers have been shown to be uniquely capable of cleaving and promoting activation of the mechanosensing adhesion GPCR EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2) encoded by adhesion G protein-coupled receptor E2 (*ADGRE2*) in vitro. A gain-of-function missense variant in *ADGRE2* has been reported in association with a severe form of familial vibratory urticaria [43], and pre-treatment of cultured mast cells with α/β -tryptase heterotetramers enabled *in vitro* activation by a vibratory stimulus, whereas β -tryptase homotetramers had no such effect [36]. One common clinical finding with H α T is cutaneous flushing and itching with vibration often being reported as a trigger [23]. Similarly, when individuals with a missense variant of *ADGRE2* were provoked by vibration of the forearm on a laboratory vortex, symptoms of localized, erythematous, edematous, and pruritic hives developed within minutes [43]. In one study examining the association between tryptase genotypes and response to vibratory challenge using a vortex, increasing ratios of germline sequence copy encoding

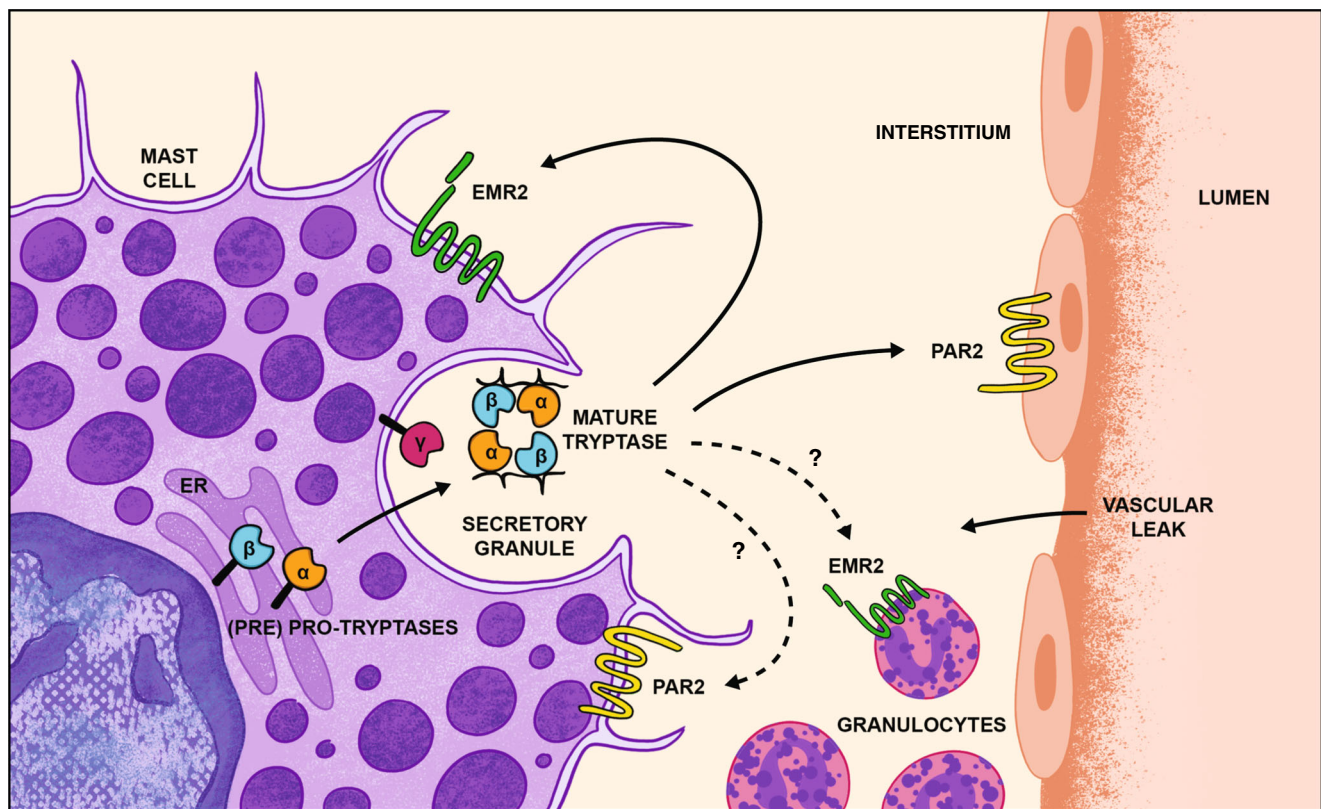


Fig. 1 Schematic of α/β -tryptase heterotetrameric activity following mast cell degranulation. Individuals with H α T have increased expression of α -tryptase that is associated with α/β -tryptase heterotetramer that is

uniquely able to cleave and activate EMR2 and PAR2 *in vitro* at concentration estimated to be physiologic. Dashed lines indicate effects that are probable but have not been proven experimentally

α -tryptase to β -tryptase were associated with more severe symptom scores among healthy volunteers and individuals with H α T [42••].

In addition to EMR2, α/β -tryptase heterotetramers have also been shown to selectively cleave and activate protease-activated receptor 2 (PAR2) on Jurkat T cells [36] at ostensibly physiologic concentrations. PAR2, which can be found on smooth muscle, neurons, and epithelial cells, is involved in modulation of inflammatory responses and has been implicated in potentiating vascular membrane permeability in the gut [44]. In Jurkat T cells, α/β -tryptase heterotetramers have been shown to be uniquely capable of inducing acute PAR2-dependent calcium flux that was not induced by homotetramers or pro-tryptases [42••]. α/β -Tryptase heterotetramers have also been shown to selectively activate PAR2 on human vascular endothelial cell monolayers resulting in acute permeability [30••]. These data demonstrate a PAR2-dependent mechanism that may lead to increased vascular leak only when activated by α/β -tryptase heterotetramers which could contribute to an increased severity of anaphylaxis, though *in vivo* studies to support this hypothesis are currently lacking.

Additional activities of mature tryptases, including anaphylatoxin generation and contact system activation, have been described that may also contribute to symptoms of immediate hypersensitivity [45–48]. Moreover, through

unspecified mechanisms, mature tryptases have been shown to enhance human mast cell histamine release, and neutralization of the enzymatic activity of mature tryptases has been shown to limit IgE-mediated temperature drop in a humanized mouse model of anaphylaxis [49••]. However, α/β -tryptase heterotetrameric activity has not been evaluated in these contexts and is likely to be challenging given the very recent evolution of human tryptases and the lack of conservation among orthologs present in murine or even non-human primate models [50].

Understanding the mechanism(s) and role(s) of tryptases in anaphylaxis is relevant to potential future efforts towards developing targeted therapies to potentially limit anaphylaxis severity. Tryptase genotyping may help identify individuals in which such future personalized therapies could be most efficacious.

Management of Immediate Hypersensitivity Symptoms in Symptomatic Individuals with H α T

H α T has been demonstrated to modify clinical symptoms of mast cell reactivity, and in up to two thirds of symptomatic individuals with this common genetic trait, phenotypes

suggestive of mast cell mediator release have been reported [23, 28, 51]. The principle clinical approaches to this point have largely been adopted from established approaches to treat mast cell mediator symptoms in patients with systemic mastocytosis and related disorders [52]. First-line treatments include oral H1 and H2 receptor blocking antihistamines, oral sodium cromolyn, or compounded ketotifen. For those individuals with elevated lipid mediators, leukotriene modifiers and/or aspirin are options, while individuals with a history of venom allergy should receive venom immunotherapy (VIT). In the latter case, if concomitant clonal mast cell disease is identified, current recommendations are for lifelong maintenance [53]. Durability of VIT and optimal duration of treatment in patients with H α T in the absence of clonal disease currently remains unknown. Other associated symptoms are often treated on an individualized basis.

Omalizumab, an anti-IgE monoclonal antibody, has been shown to have modest benefit in one small cohort study of individuals with H α T; some symptomatic improvement was reported in 12 out of 13 individuals with a median time to response of 8 weeks [54]. Symptoms such as urticaria, pruritus, abdominal pain, and food intolerance appeared to be more amenable to omalizumab therapy, whereas symptoms of autonomic dysfunction, diarrhea, and joint hypermobility did not improve. It remains unknown which symptoms may respond to specific pharmacological agents. No biomarkers have yet been identified that might herald a specific therapeutic response to a given intervention. However, there are several therapeutics in current clinical trials that may hold promise for symptomatic individuals with H α T, including monoclonal antibodies targeting SIGLEC-8 [55], IL-33 [56], and even mature tryptase [57].

Conclusions

H α T is an autosomal dominant genetic trait and a common cause for elevated BST in Western populations. H α T prevalence is increased in both clonal and non-clonal mast cell-associated disorders—including systemic mastocytosis and idiopathic anaphylaxis—where it augments symptoms of immediate hypersensitivity including anaphylaxis. Moreover, H α T is now established as a risk factor for severe anaphylaxis among individuals with venom allergy—particularly in the context of clonal mast cell disease. The unique activities of α/β -tryptase heterotetramers may contribute to these clinical associations, but additional mechanism(s) are possible. It also is likely that other clinical disorders, such as chronic urticaria and gastrointestinal diseases, may also be modified or even provoked by the presence of H α T in susceptible individuals, but this remains unproven. As additional insights into the physiologic effects of α -tryptase over-expression in humans are gained, additional pathways will be identified that may be

targeted for therapeutic benefit in symptomatic individuals with H α T.

Abbreviations *ADGRE2*, adhesion G protein-coupled receptor E2 gene; *BST*, basal serum tryptase; *EMR2*, EGF-like module-containing mucin-like hormone receptor-like 2; *H α T*, hereditary alpha-tryptasemia; *HVA*, hymenoptera venom-induced anaphylaxis; *GPCR*, G protein-coupled receptor; *PAR2*, protease-activated receptor 2; *PCR*, polymerase chain reaction; *TPSAB1*, Tryptase alpha/beta 1 gene; *TPSB2*, Tryptase beta 2 gene; *VIT*, venom immunotherapy

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Declaration

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Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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