Abstract

Hereditary α-tryptasemia (HαT) is a common autosomal dominant genetic trait with variable penetrance associated with increased serum baseline tryptase (SBT) levels. Clinical manifestations may range from an absence of symptoms to overtly severe and recurrent anaphylaxis. Symptoms have been claimed to result from excessive activation of EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2) and protease activated receptor 2 (PAR-2) receptors by α/β-tryptase heterotetramers. Herein, we aimed to review the evidence on whether HαT can be considered a hereditary risk factor or a modifying factor for anaphylaxis.

Increased SBT levels have been linked to an increased risk of anaphylaxis. Likewise, recent studies have shown that HαT might be associated with a higher risk of developing anaphylaxis and more severe anaphylaxis. The same has also been shown for patients with clonal mast cell disorders, in whom the co-existence of HαT might lead to a greater propensity for severe, potentially life-threatening anaphylaxis. However, studies leading to such conclusions are generally limited in sample size, while other studies have shown opposing results. As such, further studies investigating the potential association of HαT with anaphylaxis caused by different triggers, and different severity grades, in both patients with clonal mast cell (MC) activation syndromes and the general population are still needed.

Key words
Anaphylaxis; Hereditary alpha-tryptasemia syndrome; Tryptase; Mast cell activation syndrome; serum baseline tryptase.

IMPACT STATEMENT

The potential association between hereditary α-tryptasemia and a higher risk for anaphylaxis or more severe anaphylaxis is plausible but lacks validatory evidence in large non-selected study populations.

INTRODUCTION

Hereditary α-tryptasemia (HαT) is an autosomal dominant genetic trait with a variable penetrance (1) which is present in 4 to 6% of the general population (2). This condition is associated with an excess of copies in *TPSAB1* (2), which leads to an increased release of pro-tryptases, being the most common cause of elevated serum baseline tryptase (SBT) (1). Symptoms may result from the activation of epidermal growth factor (EGF)-like module-containing mucin-like hormone

receptor-like 2 (EMR2) and protease-activated receptor 2 (PAR-2) receptors by α/β-tryptase heterotetramers (1, 2). Whereas a significant (although unknown) proportion of HαT-carriers remains asymptomatic, HαT may present with mast cell activation-related clinical manifestations including anaphylaxis (3).

Anaphylaxis is defined as a severe life-threatening systemic/generalized hypersensitivity reaction (4, 5), with varied mechanisms, clinical presentations, and degrees of severity that results from the release of mast cell (MC)/basophil mediators (6). Widely considered to be underdiagnosed, its lifetime prevalence may reach 0.3–5.1% (7). While some factors have been established as being associated with an increased (e.g., age, allergy to nut storage proteins) or decreased (e.g., allergy to Bet v1 manifesting as oral allergy syndrome) risk for anaphylaxis due to food allergy (8), evidence on risk factors for other etiologies is limited (7).

Studies have shown a potential association between elevated SBT (a surrogate marker for HαT) and anaphylaxis (9-14), but data on this matter are still limited. Mast cell disorders are variably associated with both elevated SBT and anaphylaxis (15). In fact, several studies have defined clonal (mastocytosis and monoclonal mast cell activation syndromes) and non-clonal MC disorders (non-clonal mast cell activation syndromes) as risk factors for severe and recurrent anaphylaxis due to Hymenoptera venom allergy (HVA), drug hypersensitivity, food allergy or even idiopathic anaphylaxis (15-21). Recently, HαT has been shown to be more prevalent in patients presenting with mastocytosis (12 to 17%) and idiopathic anaphylaxis (17%) (22, 23), and the coexistence of HαT and clonal MC disorders/mastocytosis has been described as a genetic biomarker for severe anaphylaxis (23). In the general population, HαT has been associated with both a higher risk for anaphylaxis (3, 24, 25) and a higher risk for more severe anaphylaxis (22, 25). Still, recent studies do not support this claim (26, 27).

Herein, we aimed to review the evidence on whether HαT can be considered a hereditary risk factor or modifying factor for anaphylaxis and to review the pathophysiological mechanisms potentially involved.

METHODS

A literature search was carried out in the MEDLINE and Scopus databases using the PubMed search engine as of July 2022. Keywords on the query included: “Hereditary Alpha-Tryptasemia”, “elevated tryptase” and “Anaphylaxis”. The search was limited to articles published during the last ten years. No language restrictions were included. A narrative review was performed based on the relevant literature, including case reports, case series, retrospective series reviews, and narrative reviews.

Risk factor for anaphylaxis was defined as a variable associated with an increased frequency of anaphylaxis. Modifying factor for anaphylaxis was defined as a variable that can alter the severity

or clinical manifestations of anaphylaxis.

HEREDITARY α-TRYPTASEMIA

Tryptase genetics and biological role

Tryptases are serine proteases released by MC and basophils (to a lesser extent) (28). The tryptase genomic locus is located in chromosome 16p13.3 and contains four genes: *TPSG1*, *TPSB2*, *TPSAB1*, and *TPSD1* (2, 29). Although all of these genes encode tryptases, only *TPSB2* and *TPSAB1* encode isoforms that are routinely and collectively measured (α and β-tryptase) (29). Overall, tryptases derive from pre-tryptase, a 274 amino acid peptide, which is processed into pro-tryptase, a 257 amino acid peptide.

A limited amount of pro-tryptase is constitutively secreted by unstimulated MC and comprises the vast majority of SBT (30). It can also be processed into 245-amino-acid mature tryptases, which are then stored in MC granules as tetramers, being stabilized by heparin (2). Bioactive tryptase tetramers derive exclusively from *TPSB2* (which encodes β-tryptase) and *TPSAB1* (which encodes α- or β-tryptase) (30). These isoforms are extremely similar (at least 97% identical), which makes laboratory distinction of tryptase isoforms extremely difficult (29). Mature α-tryptase does not form proteolytically viable tetramers and is not stored, while mature β-tryptase tetramers are primarily present in MC cytoplasmatic granules being released following MC activation (2). Whereas β-tryptase is a well-known active protease, the role of α-tryptase is enigmatic. In fact, its homotetramers are almost devoid of proteolytic activity (31). Simultaneously, α-tryptase protomers (subunits that constitute an oligomeric protein) are thought to have allosteric effects on neighboring β-tryptase protomers, facilitating the formation of α/β-tryptase tetramers (32). This process is spontaneous in individuals who have α-tryptase-encoding genes (31) and involves a two-step proteolytic processing and stabilization by heparin proteoglycans (30). These heterotetramers have unique functional properties that can lead to the activation of MCs and other cell types, some of which may underly specific clinical manifestations of HαT and other disorders involving MCs (31). In fact, such effects are thought to derive from the cleavage and activation of EMR2 and also of PAR-2 (which is not induced by homotetramers or pro-tryptases), and from a higher stability, which results in a longer duration of action of heterotetramers when compared to homotetramers (1, 2). EMR2 activation by such tetramers has been shown to decrease the threshold for vibration-induced *in vitro* MC degranulation (2, 33). Also, heterotetramers selectively cleave and activate PAR2. This receptor which can be found on smooth muscle, neurons, and epithelial cells, is involved in the modulation of inflammatory responses and has been implicated in potentiating vascular membrane permeability in the gut (1). *In vitro* studies have suggested a PAR2-dependent increased vascular

leakage resulting from an α/β-tryptase heterotetramer activation (22). However, *in vivo* studies to support this hypothesis are currently lacking.

Pathophysiology of hereditary α-tryptasemia

HαT is characterized by an increased release of pro-tryptases due to an excess of copies in *TPSAB1* (2) and is a common cause of elevated SBT levels (1).

Canonical *TPSAB1* genotypes include 2α:2β, 1α:3β, or 0α:4β (Table 1). Individuals with HαT have additional α-tryptase alleles, which results in an n(α)β allele (1). Most individuals with HαT present with a duplication of α-tryptase (26), but as many as five extra copies of *TPASB1* have been reported (34). When the absolute copy number is not increased, SBT has been shown to increase per copy of α-tryptase encoded by *TPSAB1* (2). However, α-tryptase copy numbers are not directly correlated to SBT, as coinheritance of regulatory elements has also been hypothesized to cause SBT elevations in HαT (35).Even though HαT does not seem to be associated with a higher intracellular tryptase content (31), it may be associated with a more significant formation of α/β heterotetramers. In fact, an increased number of α-tryptase copies in *TPSAB1* seems to result in a higher ratio of α/β heterotetramers when compared to β homotetramers (2, 31). While an increased activity of α/β heterotetramers may cause symptoms associated with HαT, this association remains hypothetical and has been related to the cleavage and activation of EMR2 and PAR2 receptors. Specifically, EMR2 activation and cleavage in HαT have been associated with flushing, pruritus, urticaria, and angioedema following exposure to vibratory stimuli (1). PAR2 activation seems to increase vascular endothelium permeability (potentially causing an increase in the severity of hypotension during anaphylaxis) and smooth muscle contraction (inducing bronchospasm and/or abdominal cramping), potentially leads to neuronal activation (leading to pruritus and hyperalgesia), and to inflammation of epithelial membranes and joint synovial surfaces (31).

Clinical manifestations

Several clinical phenotypes associated with HαT have been described, with some individuals showing few or no symptoms when compared to controls from the general population (26). The so-called functional gastrointestinal complaints are among the most reported. Some of these might be difficult to characterize or quantify. Still, irritable bowel syndrome (IBS)-like symptoms, as defined by Rome III Criteria, has been reported in approximately half of the affected individuals (3, 29). Around half of the individuals also present with recurrent cutaneous symptoms, including flushing and pruritus (29). Usually, these symptoms are spontaneous, while vibration or light trauma (e.g., hand clapping) are frequently identified as triggering factors (29).

Systemic reactions consistent with IgE-mediated immediate hypersensitivity to insect venom (i.e., Hymenoptera venom allergy) were reported in approximately 20% of HαT patients (29). This

reported prevalence is four times higher than that described in the general population (36). Other reported clinical manifestations include mood swings, connective tissue abnormalities such as joint hypermobility, retained deciduous dentition, congenital anomalies, autonomic dysfunction (orthostatic hypotension, tachycardia, presyncope, and syncope), and also constitutional symptoms such as chronic pain and fatigue (2, 10, 11, 13, 14, 29, 37). In a small number of highly symptomatic families with increased TPSAB1 copies, eosinophilic gastrointestinal disease, multiple food intolerances, failure to thrive, and IgE-mediated allergies have also been described (29).

Isolated studies have shown that HαT patients may display histopathological changes, namely an increased number of MC in the small intestine (correlating with the increase in tryptase) and abnormal MC morphology and topography in both the bone marrow and small intestine (38, 39).

Diagnosis

In individuals with suspected HαT, assessment of SBT levels is the first diagnostic step. Whereas lower SBT levels have been found in patients with HαT (3), most patients present with levels above 8 ng/mL (2). Droplet-digital polymerase chain reaction (ddPCR) is currently considered the most robust and reliable method (sensitivity 100% and specificity 90%) for the detection of copy number variations in the *TPSAB1* gene, allowing its genotyping (2, 30). This technique enables detecting α- and β-tryptase-encoding sequences in *TPSAB1* and *TPSB2* at the tryptase locus (1). The ratio of α and β alleles over control-gene copies is then determined (29). These ratios are used to calculate the α/β ratio in order to obtain the patient's genotype (29). HαT is diagnosed in the presence of an increased *TPSAB1* copy number (i.e., ≥3 α-tryptase-gene copies or 2 α-tryptase-gene copies in the presence of 3 β-tryptase-gene copies) (25). The most common HαT genotypes include 2α:3β, 3α:2β, 4α:2β, 3α:3β) (2, 29) (Table 1).

Treatment

The recommended treatment of HαT manifestations is symptom-based. Therefore, asymptomatic individuals with HαT lack an indication for treatment (30). Since most symptoms are suggestive of mast cell mediator release, H1- and H2-anti-histamines, leukotriene receptor antagonists, mast cell membrane stabilizers (i.e., sodium cromolyn), high dose aspirin (in specific cases presenting with elevated lipid mediators (1)) and anti-IgE therapy (i.e., omalizumab, in patients with recurrent idiopathic anaphylaxis) have been suggested (2). Ongoing clinical trials using novel monoclonal antibodies targeting SIGLEC-8 (40-43) and tryptase (44) may add up to the symptom-directed treatment of HαT patients.

In the presence of prior anaphylaxis, self-injectable adrenaline should be prescribed (2). In patients with a history of HVA, specific immunotherapy with Hymenoptera venom (VIT) is recommended (1, 2). While lifelong VIT is recommended for clonal mast cell disorders (45) due

to a potentially higher risk of anaphylaxis with field stings following VIT discontinuation (46), it is not currently recommended in HαT, as evidence of its indication is lacking.

HEREDITARY α-TRYPTASEMIA AND ANAPHYLAXIS

Serum tryptase and anaphylaxis

Serum tryptase has been used as a sensitive biomarker for the assessment of mast cell burden in systemic mastocytosis (SM) (47) and the confirmation of acute MC activation during anaphylaxis (10), even though a subset of patients with food allergy may not present with tryptase elevation during anaphylaxis (48, 49). Traditionally, the laboratory confirmation of anaphylaxis required the elevation of acute serum tryptase levels above the normal cut-off value (i.e., >11,4 ng/mL). However, different methods for calculating serum tryptase elevation over the individual's SBT levels have been proposed for the same purpose, showing higher sensitivity and specificity (50, 51). Specifically, the 20%+2 ng/mL tryptase formula was proposed, by consensus, in 2010 to diagnose episodes of mast cell activation and to define the analytical criteria for the diagnosis of mast cell activation syndromes (50). However, while this model has shown high sensitivity for the confirmation of anaphylaxis in both children and adults (52-54), its specificity may be modest in patients with elevated SBT (51). In fact, in a recent study comparing serum tryptase level changes during anaphylaxis between atopic and HαT patients, with/without SM, the use of a 1.685 ratio (acute serum tryptase over SBT) was proposed. The latter has shown higher sensitivity and specificity values in comparison with the 20%+2 ng/mL formula (51).

Elevated baseline tryptase as a risk/modifying factor for anaphylaxis

Apart from the association between elevated acute serum tryptase levels and anaphylaxis, several studies have shown elevated SBT to be a risk factor and/or a modifying factor for anaphylaxis (9-14). Fellinger et al. (11) described patients with elevated SBT as being more prone to anaphylactic reactions caused by different triggers (i.e., insect venom, drugs, foods) compared with individuals with normal SBT. Farioli et al. (9) classified patients as being at low risk for anaphylaxis when they displayed SBT < 4 ng/mL, intermediate risk 4-7.5 ng/mL, and high risk for levels > 7.5 ng/mL. In a cohort of children with food allergy, Sahiner et al. (13) reported SBT levels of 14.5 ng/mL or more to have a 90% positive predictive value for presenting with moderate to severe anaphylaxis. Akin et al. (55) reported elevated SBT in the absence of detectable clonal mast cell disease in 12–17% of patients presenting with idiopathic anaphylaxis.

In turn, several studies in which HαT genotypes have also not been systematically assessed have shown that an increased SBT is not only associated with a higher risk for anaphylaxis but also with more severe anaphylaxis (modifying factor). Both Haeberli et al. (10) and Fellinger et al. (11) described a positive correlation between SBT and the severity of anaphylaxis in patients with

an allergy to insect venom(s). In fact, the latter study showed an absence of Ring and Messmer grade I (any mild skin, gastrointestinal, or mucosal allergic reactions) or II reactions (2 mild or any moderate skin, gastrointestinal or mucosal allergic reactions) in patients with increased levels of SBT, as opposed to a frequency of 14.2% in those with anaphylactic shock (grade 4). Sahiner et al. (13) suggested that SBT levels can predict moderate to severe anaphylaxis in children with food allergy, specifically peanut allergy, as those with nut/peanut allergy had significantly higher SBT levels and more severe symptoms compared to children with milk and egg allergy with lower SBT.

However, none of these studies included a systematic assessment of HαT genotypes or clonal mast cell disorders. Since HαT is the most frequent cause of SBT elevation, these studies might point towards a straightforward association between elevated SBT/HαT and anaphylaxis or more severe anaphylaxis, given the fact that clonal mast cell activation syndromes, another cause for SBT elevation and severe anaphylaxis are rare (56, 57).

Hereditary α-tryptasemia as a risk/modifying factor for anaphylaxis

Several studies in which HαT genotypes have been assessed have shown that patients with HαT are not only more prone to anaphylaxis (risk factor) (3, 24, 25) but also prone to more severe anaphylaxis (modifying factor) (22, 25). Giannetti et al. (3) showed that more than 50% of HαT patients present with anaphylaxis in a retrospective, consecutive cohort study of 101 HαT patients. Vasquez et al. (24) showed that among patients with congenital hypermobility disorders, those with HαT showed a tendency towards a higher risk of anaphylaxis. Lyons et al. (25) showed that HVA patients diagnosed with HαT were significantly more likely to develop systemic allergic reactions/anaphylaxis and that such reactions were more severe than those occurring in non-HαT patients. Similarly, in a cohort of individuals with an HVA, Lyons et al. (22) also found HαT to be at least twice more common in individuals with severe anaphylaxis than in the general population. However, in a sex- and age-match control study by Chollet and Akin (26), including patients from an allergy/clinical immunology department and randomly selected from a biorepository, HαT was not associated with anaphylaxis. The authors suggested that reports attributing phenotypic findings to HαT might have incurred in a referral bias, due to enrichment with patients presenting with unexplained symptoms, anaphylaxis, and postural orthostatic tachycardia syndrome, which could increase the likelihood of such patients being submitted to SBT assessment (26). Accordingly, in a study by Rama et al. (27), including a small cohort of patients with nonclonal MCAS and anaphylaxis triggered not only by Hymenoptera venom but also drug hypersensitivity, food allergy, and idiopathic anaphylaxis, HαT was not associated with more severe anaphylaxis.

Hereditary α-tryptasemia and anaphylaxis in patients with mastocytosis and other clonal mast cell disorders

Clonal mast cell disease, specifically mastocytosis/SM, consists of a group of disorders in which the frequency of anaphylaxis in adults may reach 46% and in which SBT is elevated not due to increased copies of *TPSAB1* but to an increased MC burden (47). SM in adults has also been shown to be associated with severe anaphylaxis. This association has notoriously been shown for patients with bone marrow mastocytosis (a disease subtype usually presenting with a low MC burden and, hence, lower/normal levels of SBT) and HVA (58). In this regard, it should be noted that up to one-fifth of SM patients display perfectly normal levels of SBT (47, 59-61). This finding may result from α-tryptase deficiency (i.e., 0α:4β), which is present in 29% of the general population (62).

Several studies have shown that patients with SM presenting with a relatively low bone marrow mast cell burden (i.e., indolent SM) often display discordantly high SBT levels (i.e., >200 ng/mL) (21, 63), which might explain why SBT does not fit as predicting factor on some SM progression models (63-65) (Table 2). While children with elevated SBT have been shown to be more prone to severe mast cell mediator release episodes (66, 67), this association is not evident among adults with SM, with some studies suggesting the association (15, 56) and others suggesting otherwise (20). Such findings might be explained by the heterogeneity of cohorts, as those more enriched in bone marrow mastocytosis (whose diagnosis is achieved during the diagnostic study of anaphylaxis) usually display lower levels of SBT. However, none of these studies assessed the presence of HαT genotypes.

Three studies investigated the potential association between MC mediator release episodes and HαT in SM patients. In a multicentric cohort, Lyons et al. (22) showed that patients presenting with SM and HαT are 9.5 more prone to suffer from HVA-related anaphylaxis than those with wildtype tryptase genotype. However, this cohort was particularly enriched with patients without mastocytosis skin lesions, in which HVA is the form of presentation in the vast majority of patients. Greiner et al. (23) investigated a more diverse cohort, including patients with cutaneous and/or systemic mastocytosis, showing that patients with mastocytosis and HαT are overall more symptomatic (particularly concerning cardiovascular symptoms) and more prone to HVA, as well as anaphylaxis. However, in the aforementioned study by Chollet and Akin (26) comparing SM patients with and without HαT genotypes, there was no apparent association between HαT and anaphylaxis among SM patients. Likewise, in a recent study by Rama et al. (27), cardiovascular symptoms were not more frequent among patients with clonal mast cell activation syndromes/anaphylaxis with HαT genotypes vs those with a wildtype TPSAB1 genotype.

CONCLUSIONS

MC disorders and increased SBT levels of unknown causes are both risk factors for anaphylaxis and modifying factors leading to more severe reactions. In this line, HαT was considered to potentially increase the risk and/or severity of anaphylaxis in those bearing this genetic trait, both in the general population and in patients with overlapping clonal MC disorders. However, current data on this matter results from limited cohort studies, that may be affected by a selection bias, is still scarce and, at most, conflicting. In fact, current evidence only points towards a potentially higher risk for HVA-related anaphylaxis, and recent studies have suggested that HαT is neither a risk factor nor a modifying factor for anaphylaxis triggered by any cause. Furthermore, while plausible pathogenic mechanisms have been proposed - the activation of PAR2 and EMR2 by α/β-tryptase heterotetramers - confirmatory studies that validate this hypothesis are still lacking. In summary, additional studies investigating the potential association between HαT and anaphylaxis caused by different triggers (i.e., aside from HVA) and the severity of anaphylaxis, both in the general population and in clonal MC activation syndromes, are still needed.

CONFLICT OF INTERESTS

The authors have no conflicts of interest relevant to this article to disclose.

Authorship contributions:

Conceptualization: TAR; Design: MLC, MS, MJB, FF, ASF, TAR; *Data Collection or Processing:* MS, MJB, MLC; Analysis and Interpretation: MLC, MS, MJB, FF, ASF; *First draft writing*: MLC, MS, MJB, FF, ASF*; Review and approval of the final version of the manuscript*: all authors.

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Table 1. Normal variants and common hereditary α-tryptasemia genotypes (adapted from 15).

Normal Variants		Resulting genotypes
TPSB2	***TPSAB1***	
β, β	β, β	0α:4β
β, β	β, α	1α:3β
β, β	α, α	2α:2β
Common HαT variants*		**Resulting genotypes**
TPSB2	***TPSAB1***	
β, β	β, α, α	2α:3β
β, β	β, α, α, α	3α:3β
β, β	α, α, α	3α:2β
β, β	α, α, α, α	4α:2β
β, β	α, α, α, α	4α:2β

HαT, hereditary alpha tryptasemia; ■ Parent 1 ■ Parent 2.

* HαT is diagnosed in the presence of increased TPSAB1 copy numbers (i.e. ≥ 3 α-tryptase-gene copies or 2 α-tryptase-gene copies in the presence of 3 β-tryptase-gene copies).

Table 2. Features and outcomes of studies investigating hereditary α-tryptasemia as a risk factor or modifying factor for anaphylaxis.

Study	Type of study	Population	Number of participants	Risk factor	Modifying factor
Lyons JJ, et al (2016) (25)	Prospective case-control study	Selected cohort (patients with MCAS and relatives), unselected cohorts (control population)	n=351	Yes	Yes
Lyons JJ, et al (2021) (22)	Retrospective case-control study	Patients with SM and HVA/idiopathic anaphylaxis	n=652	No	Yes
Greiner G, et al (2021) (23)	Retrospective case-control study	Patients with mastocytosis with and without HαT	n=180	Yes	Non-applicable
Chollet MB, et al (2022) (26)	Prospective case-control study	Patients under follow-up at an allergy and clinical immunology department, random biorepository control population	n=131	No	No

Vazquez M, et al (2022) (24)	Retrospective case-control study	Patients with hypermobility disorders with and without HαT	n=266	No*	Non-applicable
Rama TA, et al (2022) (27)	Prospective case-control study	Patients with MCAS and anaphylaxis caused by HVA, foods and drugs/idiopathic anaphylaxis with and without HαT	n=71	Non-applicable	No

Abbreviations: HαT, hereditary α-tryptasemia**;** HVA, Hymenoptera venom allergy**;** MCAS, mast cell activation syndromes; SBT, serum baseline tryptase; SM, systemic mastocytosis.
*This study reported a tendency toward a higher frequency of anaphylaxis in the HαT group (p=0.07)

Figure1. Proposed pathophysiological mechanisms in hereditary α-tryptasemia (HαT). In comparison with normal (wild-type, WT) mast cells (MC), those from individuals with HαT possess extra *TPSAB1* copies resulting in a more significant formation of α/β heterotetramers. Following MC degranulation, α/β heterotetramers are released, and might activate epidermal growth factor (EGF)-like module-containing mucin-like hormone receptor-like 2 (EMR2) and protease-activated receptor 2 (PAR2), inducing a decreased threshold for vibration-induced mast cell degranulation, and increasing vasopermeability and bronchial/gastrointestinal smooth muscle contraction, respectively, explaining manifestations commonly found in patients with HαT (e.g., urticaria, abdominal pain and diarrhea).