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Mast cell activation in the context of elevated basal serum tryptase: genetics and presentations

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Abstract

Purpose of Review To describe inherited and acquired genetic variants and clinical entities associated with increased basal serum tryptase (BST), distinguish these levels from those which acutely rise due to mast cell activation, and finally to characterize the association between chronically elevated basal serum tryptase and episodic mast cell activation.

Recent Findings Hereditary alpha-tryptasemia is a commonly inherited genetic cause for basally elevated serum tryptase and explains elevated BST in many individuals who do not have evidence of clonal myeloid or mast cell disease. When clonal myeloid disease is present, BST may be elevated and can be a biomarker of a number of disparate disorders of the myeloid compartment.

Summary Elevated BST is most commonly caused by hereditary alpha tryptasemia but may also be indicative of clonal myeloid disease. Clinical reports suggest that elevated BST is associated with increased risk for more severe systemic allergic reactions to a number of eliciting agents and exposures. Additional studies are needed to determine the role that inherited or acquired genetic variants associated with elevated BST and clonal or non-clonal myeloid diseases may play in these reactions.

Keywords Hereditary alpha tryptasemia · BST · Anaphylaxis · Mastocytosis · Myeloid

Introduction

Heritable and acquired genetic variants account for elevated basal serum tryptase (BST) in the large majority of individuals in Western populations where this has been studied. Hematologic diseases such as systemic mastocytosis, myeloid hypereosinophilic syndromes, and myeloid leukemias have long-established clinical associations with elevated BST and in some cases increased mast cell reactivity. The recent identification of the genetic trait hereditary alpha tryptasemia has both provided some additional insights and raised questions about the nature of basal tryptase levels and clinical phenotypes classically associated with elevated BST. Significant acute rises—defined as a 20% increase over baseline + 2 ng/mL—in serum tryptase are considered diagnostic of mast cell activation most commonly due to systemic immediate hypersensitivity reactions, or anaphylaxis. However, higher basal tryptase levels have been associated with more severe clinical mast cell reactivity in a number of settings. This review will examine the various known somatic and inherited genetic causes for elevated BST and discuss what is known about symptoms of mast cell activation in these groups of individuals.

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Mediators and evaluation of mast cell activation

Historically, there has been inconsistent application of diagnostic criteria for even the most severe systemic form of mast cell activation, namely anaphylaxis. Although anaphylaxis was first described by Portier and Richet in 1902 [1], it was not until 2005 that consensus was reached on clinical criteria to define the clinical diagnosis of anaphylaxis [2]. When a

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clear trigger is not immediately evident, or symptoms are not classical in timing or presentation, the diagnosis of anaphylaxis and/or mast cell activation can still be challenging. Some clinical presentations that can present with features suggestive of anaphylaxis such as infusion reactions and hereditary angioedema may not be caused by mast cell degranulation [3, 4], and even the best available biomarkers utilized for identifying mast cell degranulation may not substantially increase in the sera of patients during true IgE-mediated severe anaphylaxis [5•, 6].

Following mast cell activation, mast cell secretory granules containing a number of pre-formed mediators are released leading to some of the symptoms commonly attributed to mast cell activation [7]. Tryptase is the most abundant granule protein [8] and has a longer half-life in serum (90–120 min) relative to other mediators such as histamine (1–6 min). A total serum tryptase level measured within approximately 4 h (two-half-lives) of symptom onset is currently the most specific laboratory test available to confirm the clinical diagnosis of a mast cell-mediated immediate hypersensitivity reaction. However, basophils also express and release tryptase with activation [9, 10], and other clonal cells within the myeloid lineage may express tryptases [11], potentially limiting the sensitivity and theoretical specificity of this assay. Additional mediators such as urinary prostaglandins (e.g., PGD2 and metabolites) and histamine metabolites (e.g., N-methylhistamine) have been studied as biomarkers of mast cell degranulation; however, these do not appear to have greater sensitivity, and particularly in the case of lipid mediators, are not mast cell-specific which may introduce confusion during diagnostic testing.

Current consensus recommendations define an acute rise in serum tryptase of 1.2 × BST + 2 ng/mL as clinically significant and consistent with severe systemic mast cell degranulation [12]. While this calculation has a high positive predictive value for anaphylaxis, the negative predictive value varies with both reaction severity and causative agent. When utilizing tryptase as a marker of mast cell activation in even a highly controlled venom sting challenge setting, acute rises in serum tryptase levels may be insufficient to achieve the current consensus criteria for mast cell activation (e.g., 1.2 × BST + 2 ng/mL) [13]. This discordance is most often observed when reactions are less severe (e.g. in the absence of hypotension) or when the blood collection is inappropriately timed. Among eliciting agents, food-allergic reactions are one of the most common causes of anaphylaxis reported with minimal changes in serum tryptase. In one study of peanut allergic adults, median tryptase levels increased more than 70% above baseline [5•]; however, most patients failed to achieve the consensus threshold for mast cell activation due to low BST levels (median ~ 4 ng/mL). Among shrimp-allergic patients, small but reproducible increases in serum tryptase during food allergic reactions were reported in 12 cases of anaphylaxis during food challenge, yet only four met consensus criteria, despite a median 40% increase over BST levels in the cohort [6]. The reasons for the variability in BST changes in clinically diagnosed anaphylaxis are as yet unclear, and the lack of definite correlation between BST and mast cell activation symptomatology frustrates both patients and clinicians alike, underscoring the need for more sensitive and specific biomarkers for mast cell activation.

Tryptase biology and genetics

Tryptases are trypsin-like proteases expressed by the allergic effectors, tissue mast cells, and blood basophils [9, 14, 15]. Tryptases require step-wise proteolytic processing and stabilization by heparin proteoglycans, in order to form mature tetrameric enzyme [16]. Once formed, stabilized tetramers—called "mature" tryptases—are stored in secretory granules with other allergic mediators and released during degranulation following cellular activation [17].

Of the five known genes encoding human tryptases, only α-tryptase encoded at *TPSAB1* and β-tryptases encoded at *TPSAB1* and/or *TPSB2* are believed to comprise serum tryptase [18]. The frequency of alleles containing α-tryptase isoforms encoded at *TPSAB1* is highly variable depending upon racial or ethnic make-up of any given population. While this has not yet been extensively studied, greater numbers of α-tryptase containing alleles are seen among individuals of Asian descent and are less common among individuals of African descent [19]. In the USA, it is estimated that approximately one-third of individuals possess only β-tryptase encoding sequences at *TPSAB1* and *TPSB2*, and thus are α-tryptase deficient [19]. A frameshift mutation has also been reported in an isoform of β-tryptase (βIII) predominantly present at the *TPSB2* locus which, if expressed, is predicted to have negligible proteolytic activity [19].

In the absence of acute mast cell activation, serum tryptase is composed of pro-tryptases which are constitutively secreted by mast cells in tissue and diffuse into the systemic circulation [17, 18]. While the serum half-life of mature tryptases derived from secretory granules is well-characterized as 90–120 min [20], the serum half-life of pro-tryptases remains unknown [21]. The median total tryptase level in human serum is approximately 5 ng/mL; in healthy asymptomatic individuals, this level is composed only of pro-tryptases with mature tryptase being undetectable. The upper limit of normal for serum tryptases is currently defined as 11.4 ng/mL. This cutoff was established by calculating the 95% confidence interval of a normal distribution centered on 5 ng/mL in an otherwise right-skewed population following elimination of the long positive tail (Fig. 1). However, this level can increase substantially during systemic immediate hypersensitivity reactions or anaphylaxis, where the rise is caused by release of mast cell granule contents containing predominantly, if not exclusively,

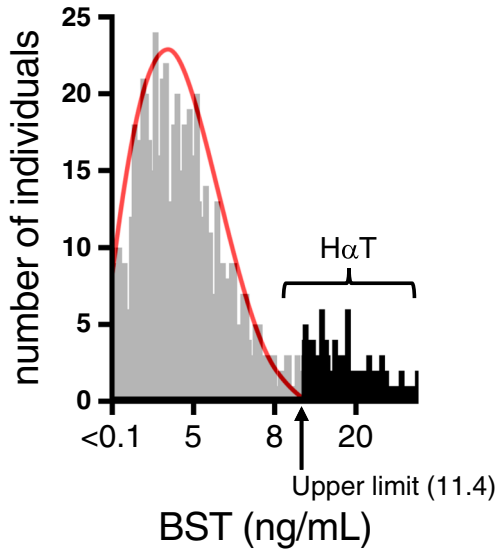

Fig. 1. Distribution of basal serum tryptase. Basal serum tryptase (BST) levels among a cohort of individuals studied within the Laboratory of Allergic Diseases at the NIH Clinical Center, demonstrating a multimodal distribution, made more evident by inclusion of a large group of individuals with hereditary alpha tryptasemia (HαT). Super-imposed normal distribution curve (red) that is derived from the majority of individuals that do not have increased *TPSAB1* copy number and follow a near-normal distribution (grey) centered around ~ 5 ng/mL, after exclusion of the right-skewed tail (black).

mature tryptases. The assay that is specific for mature tryptase is not widely available clinically and no clinical assay yet exists that can distinguish between α- and β-tryptases. Thus, when a serum tryptase level is reported clinically, the measurement reflects total tryptase, composed of pro and mature α- and β-tryptases.

While there is a substantial body of literature examining the effects of mature tryptases on cellular signaling and phenotypes both *in vitro* and in animal models, clear correlation with human disease phenotypes has been lacking. Both inhaled and oral tryptase inhibitors have been studied in early phase clinical trials for asthma and ulcerative colitis, respectively. However, both programs were ultimately abandoned due to lack of clinical efficacy [22, 23]. In the context of mast cell mediator symptoms, such as anaphylaxis, it is believed that mature tryptases may contribute to associated vascular leakage symptoms [24, 25]. However, mature α-tryptase homotetramers have negligible proteolytic activity [26], raising the question of how increased α-tryptase expression, as seen in HαT, might contribute to associated clinical phenotypes such as urticaria and anaphylaxis. One examination of mature tryptases has shed light on this, demonstrating unique biophysical and proteolytic properties of newly identified naturally occurring α/β-heterotetrameric mature tryptases [27••]. Unlike homotetrameric α- or β-tryptases, heterotetramers were able to cleave and activate protease-activated receptor-2 (PAR2) and EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2). Because an activating mutation in *ADGRE2* encoding EMR2 has been associated with familial vibratory urticaria [28], the authors went on to demonstrate an association between tryptase protomer composition (i.e., tryptase genotype) and physical urticaria, where increasing numbers of α-tryptase encoding *TPSAB1* copies were associated with increased cutaneous responses to vibratory challenge. Large-scale examination of tryptase genotypes among individuals with other mast cell-related disorders has not yet been undertaken to determine whether other outcomes or phenotypes may be affected by tryptase genotype.

Conditions leading to elevated basal serum tryptase

Hereditary alpha tryptasemia (HαT) and other inherited conditions

Among populations in whom individual BST levels have been studied, approximately 5–7% of individuals have a BST level above 11.4 ng/mL—the upper limit normal in most laboratories [29, 30]. Most of these studies were Caucasian cohorts and, in most individuals, a genetic trait called hereditary alpha tryptasemia (HαT) is likely causative. HαT results from increased germline copies of *TPSAB1* encoding α-tryptase [31•] with as many as four extra copies of *TPSAB1* having been reported in one family [32]. With increasing *TPSAB1* copy number, a gene-dosage effect has been reported both on BST levels and on associated clinical phenotypes such as abdominal pain and diarrhea and cutaneous flushing, pruritus, and hives. One additional *TPSAB1* copy results in an average BST level of 15 ± 5 ng/mL, two extra copies 24 ± 6 ng/mL, and in the family with four extra copies 37 ± 14 ng/mL [33].

Because all individuals with HαT reported to date have BST levels > 8.0 ng/mL, this genetic trait is believed to have complete penetrance, while expressivity appears to be variable [33] (Table 1). In the limited studies examining HαT, approximately half of reported individuals presented with a multisystem, or syndromic presentation that has been called HαT syndrome (HαTS) [31•, 32, 34] (Table 2). In a large Austrian cohort study examining individuals with elevated BST levels of unknown cause, similar symptoms were likewise reported to have increased prevalence among affected individuals [29]. Many of these symptoms are commonly seen in the context of mast cell-associated disorders [35–37], and a small number have been validated in unselected individuals with HαT [31•]. Some of these phenotypes, such as connective tissue abnormalities including joint hypermobility and symptoms suggestive of autonomic dysfunction, were observed in primary cohorts of individuals with HαT and are frequently reported among individuals presenting with symptoms suggestive of mast cell activation. However, these findings have not yet been validated in unselected populations of individuals with HαT (Table 1) and the degree to which mast cells may contribute to many of these symptoms remains unknown.

Table 1 Clinical features reported in association with hereditary alpha tryptasemia (HαT)

Manifestation	Reported prevalence[a]	Association supported in an unselected cohort[b]
Basal serum tryptase > 8 ng/mL	100%	Yes
Chronic gastroesophageal reflux symptoms	56–77%	No
Arthralgia	44–45%	No
Body pain/headache	33–47%	No
Flushing/pruritus	32–55%	Yes
Irritable bowel syndrome (Rome III)	28–49%	Yes
Sleep disruption	22–39%	No
Systemic immediate hypersensitivity reaction	21–28%	No
Retained primary dentition	20–33%	Yes
Systemic venom reaction	14–22%	Yes
Congenital skeletal abnormality	11–26%	No
Joint hypermobility	0–28%	No
Positive tilt-table test	0–11%	No

[a] In order of reported prevalence, ranges are derived from available data in three reports [29, 30, 32]

[b] Finding was identified as significantly associated with increased *TPSAB1* copy number in an unselected volunteer adult population

Table 2 Causes for elevated basal serum tryptase[a]

Heritable causes
- Hereditary alpha tryptasemia
- GATA2 haploinsufficiency[b]
- Gaucher's disease (*GBA* loss-of-function)

Acquired causes

Clonal mast cell disease
- Mastocytosis
  - cutaneous
  - systemic
  - mastocytoma
- Mast cell sarcoma

Myeloproliferative or Myeloid disease
- Hypereosinophilic syndromes
  - myeloid variant
  - idiopathic
- Chronic eosinophilic leukemia
- Myelodysplastic syndrome
- Myelofibrosis and refractory anemias
- Myeloid leukemias

Other
- Renal failure
- Parasitic infection
- Eosinophilic gastrointestinal diseases[c] (e.g., EoE)

[a] Mast cell activation in these conditions can also result in an acute rise in serum tryptase

[b] Elevated BST may result from clonal myeloid disease

[c] May be an association rather than cause

Of the symptoms more likely to be related to mast cell mediator release, recurrent cutaneous symptoms consisting of flushing, pruritus, and/or different forms of urticaria have been reported by up to half of the individuals described with HαT. The somewhat more common findings of urticaria and/or angioedema among individuals with HαT are present in contrast to patients with clonal mast cell disorders who rarely present with swelling or hives. Moderate to severe anaphylaxis, most commonly caused by stinging insects, has been reported in 14–22% of HαT individuals studied, a rate approximately half that which has been reported among individuals with clonal mast cell disease [38–40]. Furthermore, HαT may be seen in patients with clonal mast cell disease [32], thus for patients with idiopathic and venom anaphylaxis, or severe anaphylaxis regardless of cause, we currently advocate for evaluation of mastocytosis regardless of tryptase genotype.

While increased *TPSAB1* copy number is the most common heritable genetic cause for increased BST identified to date, there are a few additional single-gene disorders that have been identified to be associated with elevated basal levels. One individual with a heterozygous loss-of-function mutation in *GBA* encoding Glucocerebrosidase, resulting in Gaucher's disease (GD), has been reported with elevated BST [41]. The patient had developed immediate hypersensitivity to the enzyme replacement product imiglucerase and was started on an alternative enzyme replacement product, but BST elevations persisted. The relationship between glucocerebrosidase deficiency and mast cell reactivity or tryptase expression remains unclear.

GATA2 haploinsufficient patients who present with a number of protean manifestations also frequently present with elevated BST [42]. Because of the critical importance of GATA2 for

maintenance of many hematopoietic lineages including mast cells, affected individuals frequently present with progressive bone marrow failure, with mast cells in bone marrow and tissues being largely spared in number for unclear reasons. Despite this, GATA2 insufficiency also results in reduced KIT and FcεRI on the surface of mast cells, as well as B cell dysfunction with low total and antigen-specific IgE. As a consequence, GATA2 haploinsufficient patients actually have reduced mast cell reactivity and clinical allergy. Furthermore, given the propensity for these patients to develop myeloid malignancies, it remains unclear whether elevated BST levels are in fact arising from mast cells, or rather from non-mast cell myeloid clones, as can be seen in other myeloproliferative disorders.

Mastocytosis and clonal mast cell disorders

The archetypal acquired disorder associated with elevated BST is the clonal mast cell disease mastocytosis [43]. This neoplasm can be limited to the skin (cutaneous mastocytosis) or involve extracutaneous tissues (systemic mastocytosis). WHO criteria have been established and revised over time in order to categorize the diagnoses of systemic and cutaneous disease [44]. Both forms have a number of phenotypic subcategories.

In children, disease is more often confined to the skin, whereas in adult-onset mastocytosis, most individuals with cutaneous lesions have systemic and more severe disease [45]. Among children with cutaneous disease, those with urticaria pigmentosa—pink to tan macular lesions comprised of dense mast cell infiltrates—tend to lack systemic symptoms, with disease manifestations primarily characterized by flushing, itching, and in some cases development of nodular and/or blistering lesions. Children with more diffuse cutaneous disease are reported to be at higher risk for systemic anaphylactic reactions with hypotension and shock, likely suggestive of systemic involvement [46]. Additional symptoms that may be related to mast cell mediator release such as abdominal pain and distension are much more common in adults than children, and when present in children, are also most frequently reported in those with systemic disease [45].

Clonal mast cell disease is strongly associated with severe anaphylaxis. This includes both idiopathic and antigen-mediated anaphylaxis, in particular following envenomation by stinging insects [38–40]. In a large number of otherwise healthy adults, severe anaphylaxis has been reported as the initial presenting symptom of clonal mast cell disease and in addition to insect stings, may also be caused by food antigens or medication hypersensitivity [40]. Importantly, this may occur in the absence of elevated BST. It is estimated that the lifetime prevalence of anaphylaxis among adults with systemic mastocytosis is approximately 50%. This prevalence is double that reported in HαT, and at least ten times higher than estimates for Western general adult populations [47, 48]. The reported prevalence in pediatric mastocytosis patients is between 1 and 10%, greater than the general population, but lower than that reported among adult patients, likely reflecting the increased prevalence of isolated cutaneous disease in children [49].

The majority of individuals with systemic mastocytosis and up to 15% of individuals with cutaneous disease present with BST levels of greater than 20 ng/mL [50], and this has become one of four minor criteria used for diagnosing systemic disease. While consensus recommendations for the diagnosis of systemic mastocytosis do not currently take tryptase genotyping into account, data suggest that in the absence of increased *TPSAB1* copy number, a threshold lower than 20 ng/mL may identify individuals with clonal disease, whereas among individuals with HαT, BST > 20 ng/mL is less likely to be a reliable diagnostic criterion.

There are some individuals with symptoms associated with mast cell mediator release in which one or two findings consistent with clonal mast cell disease are present—namely the gain-of-function *KIT* p.D816V missense variant and/or aberrant expression of CD25. A majority of these patients have been identified to have elevated BST. However, serum BST levels and mast cell burden in tissues of some patients are inadequate to achieve the diagnosis of mastocytosis [51]. These patients are currently defined as having monoclonal mast cell activation syndrome (MMAS) and presenting symptoms largely emulate those seen in systemic mastocytosis patients.

Hypereosinophilic syndromes and myeloid neoplasms with eosinophilia

Hypereosinophilic syndromes are characterized as persistent eosinophilia with ≥ 1500 cells/μL in peripheral blood and evidence of related tissue inflammation and damage. While elevated BST is not a criterion for diagnosis, increased numbers of mast cells and elevated BST are frequently identified among individuals with myeloid hypereosinophilic syndrome (MHES) and *PDGFRA*-associated myeloid neoplasms [52, 53]. Bone marrow mast cells from these patients do not usually form dense mast cell aggregates as seen in mastocytosis, but they may have > 25% spindle-shaped mast cells and immunophenotyping of mast cells by flow cytometry may show expression of CD25—findings that are both typically associated with clonal mast cell disease [54].

Elevated BST has been reported to occur in approximately 20% of individuals with idiopathic HES. However, among individuals with lymphoid variant HES, BST levels are generally within the normal range, suggesting that elevated BST may identify myeloid-associated disease in individuals otherwise classified as idiopathic [52, 55, 56]. Whether these individuals may have an indolent form of myeloid HES or clonal mast cell disease with hypereosinophilia is unknown. Elevated BST levels have also been reported among individuals with hypereosinophilia of undetermined significance in

the absence of associated pathology, as well as in some patients with eosinophilic gastrointestinal diseases [57].

Mast cell-related symptoms have not been systematically characterized in HES patients. However, a dramatic example of concomitant hypereosinophilic disease and mast cell-mediated pathology was reported in two unrelated children with the same somatic *STAT5B* p.N642H missense variant resulting in gain-of-function [58•]; a variant that is frequently associated with leukemia [59]. These two patients had very high variant allele frequencies that were present in all examined hematologic lineages suggesting the somatic disease was acquired in a multi- or pluripotent progenitor. Both affected children reported recurrent idiopathic flushing and chronic spontaneous urticaria. Recurrent immediate hypersensitivity reactions to foods and stinging insects were also reported in one of the two affected individuals, and both had recurrent bouts of abdominal distension and/or diarrhea that may have been related to mast cell and/or eosinophil-driven pathology.

Myeloproliferative disorders

Not only clonal diseases in mast cells and eosinophils, but somatic mutations leading to clonal expansion of other myeloid-lineage cells are also frequently associated with elevated BST. Up to 40% of patients with acute and chronic myeloid leukemia (AML and CML) have been reported with elevated BST [11, 60]. Interestingly, it appears that in many individuals, elevated BST is associated with over-expression of *TPSAB1* by malignant myeloblasts from AML [56, 60–62], juvenile myelomonocytic leukemia (JMML) [63], and CML [64] patients. Generally, these myeloproliferative neoplasms are distinguishable from individuals with ISM or myeloid HES on the basis of clinical presentation; however, systemic mastocytosis may rarely be seen in association with another hematologic neoplasm. Absent this association, the prevalence or nature of clinical findings suggestive of mast cell activation among individuals with myeloproliferative diseases outside of the mast cell lineage remains largely undefined. A potential exception may be polycythemia vera, most frequently associated with the recurrent gain-of-function *JAK2* missense p.V617F, wherein intense pruritus—typically aquagenic—is reported in approximately half of affected individuals [65]. The cause for this clinical finding remains uncharacterized, but mast cells have been implicated [66–68] despite BST levels rarely being elevated in these patients [11].

Elevated BST of unknown etiology and mast cell activation

In several studies where the cause for BST elevation was not characterized, a strong association with severe anaphylaxis to stinging insects (e.g., hymenoptera species) has been reported [29, 38, 69–71]. While many of the individuals with elevated BST and venom anaphylaxis have clonal mast disease as the underlying cause, individuals with venom allergy have not been systematically evaluated for other causes of BST elevation such as HαT. Moreover, this association may not be limited to venom. At least one study among otherwise healthy Brazilians has demonstrated a similar association of elevated BST with anaphylaxis severity independent of the causative agent [72]. Another study in food-allergic children—ostensibly less likely to have clonal mast cell disease—demonstrated a positive correlation between BST and anaphylaxis severity and found that a BST level > 14.5 ng/mL had a 90% predictive value for identifying children with moderate to severe anaphylaxis to foods [73]. Two additional studies reported that elevated BST was present in 12–17% of individuals with idiopathic anaphylaxis in whom clonal mast cell disease was not identified, a level double what has been reported in the general population [74, 75]. Finally, in two retrospective studies, anaphylaxis was reported in 21–36% of individuals with elevated BST [29, 76]. Though these individuals were not evaluated for clonal mast cell disease, it is unlikely to have fully explained the association. The larger of the two studies reported approximately 1.3% of the total complement of patients seen at a general clinical allergy practice in Austria (~ 200 individuals) to have BST > 11.4 ng/mL. This prevalence, if due to clonal mast cell disease, would be approximately one hundred times higher than current estimates for the prevalence of mastocytosis [77].

Beyond anaphylaxis, BST levels have also been found to be higher in CsU patients compared to both non-atopic and atopic subjects. The highest levels were reported among those with more active disease, despite mature tryptase (i.e., evidence of mast cell degranulation), being undetectable in those patients [78].

Conclusions

The discovery of hereditary alpha-tryptasemia—a commonly inherited genetic cause for basally elevated serum tryptase—has provided an explanation for elevated BST in many individuals who do not have evidence of clonal myeloid or mast cell disease. When clonal myeloid disease is present, BST is often elevated and can be a biomarker of these disorders. However, mastocytosis may be present in patients with normal tryptase, in particular children with cutaneous disease. Epidemiologic studies demonstrate that elevated BST is associated with increased risk for more severe systemic allergic reactions to a number of eliciting agents and exposures and may be associated with more persistent or severe cutaneous symptoms including chronic pruritus and urticaria. While individuals with mastocytosis clearly contribute to many of these associations, and are often reported with the most

profound phenotypes, clonal disease alone is unlikely to account fully for the clinical data. Additional studies are needed to determine the role that inherited or acquired genetic variants associated with elevated BST and clonal or non-clonal myeloid diseases may play in associated phenotypes such as pruritus, urticaria, and anaphylaxis, and whether tryptase directly contributes to these and other clinical symptoms.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations HαT, Hereditary alpha tryptasemia; BST, Basal serum tryptase; PAF, Platelet activating factor; EMR2, EGF-like module-containing mucin-like hormone receptor-like 2; *TPSAB1*, Tryptase alpha/beta 1 gene; *TPSB2*, Tryptase beta 2 gene; GBA, Glucosylceramidase; GATA2, GATA binding protein 2; *JAK2*, Janus kinase 2 gene; STAT5b, Signal transducer and activator of transcription 5b; *KIT*, KIT proto-oncogene receptor tyrosine kinase; MMAS, Monoclonal mast cell activation; PAR, Protease activated receptor; *FIP1L1/PDGFRA*, FIP1-like-1/platelet-derived growth factor receptor-α fusion gene; HES, Hypereosinophilic syndrome; AML, Acute myeloid leukemia; CML, Chronic myeloid leukemia; JMML, Juvenile myelomonocytic leukemia; CsU, Chronic spontaneous urticaria; ISM, Indolent systemic mastocytosis

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- • Of importance
- •• Of major importance

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