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Hereditary alpha tryptasemia: literature overview on the genetic trait and its clinical manifestations

Agnieszka Rydz[1], Magdalena Lange[2]

[1]*Student's Scientific Circle Practical and Experimental Dermatology, Medical University of Gdańsk, Poland*
[2]*Department of Dermatology, Venereology and Allergology, Medical University of Gdańsk, Poland*

ABSTRACT

Hereditary Alpha Tryptasemia (HαT) is a genetic condition characterized by an increased number of copies of the *TPSAB1* gene, resulting in elevated basal serum tryptase levels and an increased risk of anaphylaxis, especially in individuals with IgE-dependent allergies or systemic mastocytosis. The severity of clinical symptoms can vary and is influenced by the number of extra *TPSAB1* gene copies, suggesting a gene-dose effect. Approximately two-thirds of individuals with HαT show minimal or no symptoms. The remaining individuals with HαT may present with *Hymenoptera venom* allergy, flushing, urticarial/angioedema, irritable bowel syndrome, gastrointestinal reflux, hypermobility, neuropsychiatric symptoms and dysautonomia.

Recent studies revealed that α-tryptase which forms complexes with β-tryptase activate protease-activated receptor-2 (PAR2) receptors. Activation of these receptors may lead to hypotension, muscle contraction, inflammation, and trigger neuropeptide secretion, and in consequence, result in mast cell degranulation. This cycle of activation and degranulation may potentially contribute to the development of mast cell activation syndrome (MCAS).

Mast cell activation syndromes are defined by systemic, severe and recurrent mast cell activations, usually in the form of anaphylaxis. Hereditary/familial MCAS is a specific subtype of MCAS, which is associated with HαT.

Diagnostic work-up for HαT includes determination of basal serum tryptase level and the presence of additional *TPSAB1* gene copies using droplet digital polymerase chain reaction.

Further research is needed, to explore the relationship between HαT and MCAS, as well as to determine if there is a distinct form of hereditary MCAS which is independent of HαT. These investigations aim to improve diagnostic approaches and treatment strategies for individuals with HαT, enhancing their management and overall quality of life.

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Keywords: hereditary alpha tryptasemia, HAT, familial/hereditary MCAS

INTRODUCTION

Hereditary alpha tryptasemia (HαT) is an autosomal dominant genetic trait caused by an increased number of copies of the *TPSAB1* gene, which encodes for alpha-tryptase. The estimated frequency of HαT is 3–5.5% within the Western and predominantly Caucasian population [1–3]. This condition, first described in 2016, is a common cause of elevated basal serum tryptase (BST) — currently defined clinically as >11.4 ng/mL — and is associated with various clinical symptoms [4]. HαT patients may present with systemic immediate hypersensitivity reactions, particularly *Hymenoptera venom* allergy, pruritus, flushing, urticarial/angioedema, joint hypermobility, connective tissue disorders, functional gastrointestinal diseases, neuropsychiatric symptoms, and dysautonomia [4–6]. The diversity and severity of symptoms vary among affected individuals, with some experiencing milder manifestations and others displaying more pronounced symptoms. Studies have shown that the severity of symptoms in HαT patients is positively correlated with the number of *TPSAB1* gene copies, which suggests a gene-dose effect [5, 6].

Individuals with HαT are at an increased risk of developing mast cell activation syndrome (MCAS) which is defined by systemic, severe and recurrent mast cell activations, usually in the form of anaphylaxis, a substantial, event-related increase of serum tryptase level beyond the individual's baseline and a response of the symptoms to medicines directed against mast cells or antimediator therapy [7].

Address for correspondence:
Agnieszka Rydz, Student's Scientific Circle Practical and Experimental Dermatology, Medical University of Gdańsk, Smoluchowskiego 17, 80–214 Gdańsk, Poland, e-mail: agnieszka.rydz@gumed.edu.pl

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The association between HαT and MCAS is particularly significant when HαT coexists with IgE-dependent allergies or systemic mastocytosis (SM) [8, 9]. In such cases, the risk of anaphylaxis and severe allergic reactions is heightened [7].

The relationship between HαT and MCAS has gathered attention in the medical community, leading to the identification of a specific subtype of MCAS known as hereditary/ /familial MCAS or HαT + MCAS. In this subtype, MCAS is not attributed to any allergies or underlying clonal MC disease, but the diagnostic criteria for MCAS and HαT are met [7]. However, it is still being investigated whether a distinct form of hereditary MCAS exists independently of HαT.

This review aims to provide a comprehensive understanding of HαT including its clinical manifestations and the correlation between HαT and MCAS.

MAST CELLS AND MEDIATORS

Mast cells (MCs) are bone-marrow-derived immune cells located in peripheral tissues, particularly those near the external environment, such as the skin, airways and gastrointestinal tract [6, 10, 11]. Mast cells are the main effectors in type I allergic reactions and diseases such as urticaria, asthma, anaphylaxis, rhinoconjunctivitis and allergic rhinitis [12, 13]. Mast cells are primarily activated by IgE-antigen complexes bound to the FcεRI receptor on their surface. This interaction leads to the degranulation of MCs and the release of MC-derived mediators including histamine, cytokines, chemokines, and proteases including tryptase, which is the most specific MC product [14]. The role of MCs and MC-mediators is to further activate an immune system and to provide various adaptive immune responses by affecting T-cells and lymph node activity [15].

Mast cells can be activated in different tissues. In the gastrointestinal tract, MC activation leads to increased fluid secretion, smooth muscle contraction, and peristalsis resulting in cramps, vomiting or diarrhoea [16]. In the respiratory tract, mast cell activation (MCA) causes airway constriction, increased mucus production, and coughing. In the skin, MC activation results mainly in the occurrence of urticaria (hives), angioedema and flushing [17].

TRYPTASE AND ITS ISOTYPE DIFFERENCES

Tryptase is a protein produced by MCs and basophils [14, 18, 19]. These cells store mature tryptases in secretory granules, where they are present as tetrameric serine protease [20]. The primary function of tryptase is its involvement in allergic inflammation, as occurs in type I immediate hypersensitivity reactions, where mature tryptases are released from MCs secretory granules with other MC-derived mediators. The proteins that have not undergone enzymatic conversion into mature tetrameric tryptases are known as protryptases [21]. These monomeric proteins are consistently secreted into the serum and constitute a significant portion of the measured BST [22].

Four types of tryptase have been identified, including three soluble forms (α, β, and δ) and one membrane--anchored form (γ) [22]. The first two isoforms are essentially unique to humans, as they have undergone important evolutionary modifications, such as duplications, gene conversions missense and nonsense mutations [22, 23].

The human tryptase locus on chromosome 16 contains four paralogous genes (*TPSG1*, *TPSB2*, *TPSAB1*, and *TPSD1*) [22]. *TPSAB1* gene can produce either alpha-tryptase or beta--tryptase. On the other hand, the *TPSB2* gene encodes only beta-tryptase [24, 25]. It is important to note that approximately one-third of individuals lack alpha-tryptase, while no one has been reported to lack beta-tryptase [22, 23, 26].

HαT is defined by the presence of extra copies of alpha-tryptase encoding sequences on a single allele in approximately 5% of individuals [15, 26–30]. The presence of extra copies of alpha-tryptase encoding sequences is associated with elevated basal serum tryptase (BST) levels currently defined clinically as >11.4 ng/mL. This increase in BST levels is likely influenced by unidentified modifiers of gene expression specific to the alpha-tryptase encoding replications [22]. Beta-tryptase, despite its similarities, does not exhibit the same clinical effect as alpha-tryptase. Therefore, variations in beta-tryptase copy numbers alone do not lead to increased BST levels [22].

PATHOGENESIS AND CLINICAL MANIFESTATIONS OF HαT AND FAMILIAL/HEREDITARY MCAS

Recently, Le QT, et al. [25] conducted a study revealing that, unlike β-tryptase, α-tryptase tetramers lack protease activity. The researchers demonstrated that the expression of α-tryptase in individuals leads to the natural formation of heterotetramers, consisting of two α-tryptase and two β-tryptase protomers, known as α/β-tryptase. These α/β--tryptase complexes specifically activate protease-activated receptor-2 (PAR2), which is found in various cell types including smooth muscle, neurons, and endothelium. Stimulation of PAR2 during MC degranulation can lead to various clinical effects. For instance, in systemic anaphylaxis, activation of PAR2 on vascular endothelium may worsen hypotension [25]. In conditions like inflammatory bowel disease and asthma, PAR2 activation on smooth muscle can result in muscle contraction, further exacerbating symptoms [31, 32]. Also, activation of PAR2 on keratinocytes and sensory nerves in the skin might intensify inflammation, pruritus, and hyperalgesia [33–36]. In addition, activation of PAR2 on sensory nerves has been found to result in the secretion of neuropeptides such as Substance P and calcitonin gene-related peptides [37]. These neuropeptides then bind to specific receptors on MCs, which triggers further degranulation

[13, 38]. This cycle of activation and degranulation may potentially contribute to the development of MCAS. These findings suggest that HαT is strongly connected with hereditary/familial MCAS presenting similar symptoms.

Based on Lyons JJ. Study [20], systemic immediate hypersensitivity reactions to stinging insects were found to be 20% more common among individuals with HαT. Moreover, flushing, pruritus, chronic gastroesophageal reflux, arthralgia, body pain, irritable bowel syndrome and sleep disruption were the most common complaints reported in symptomatic individuals.

The symptoms of MCA may resemble those of HαT and may vary among individuals. Typical clinical symptoms of MCA include pruritus, flushing, urticaria, angioedema, nasal congestion, wheezing, cough, diarrhoea, headache, and hypotension which may occur in various diseases [7].

MAIN DIAGNOSTIC FEATURES OF HαT AND FAMILIAL/HEREDITARY MCAS

The diagnosis of HαT involves several key factors as described in the Lyons study [20]. When considering HαT as a possibility, the primary indicator is BST over 8 ng/mL. This typically comes to attention following evident allergic reactions, anaphylaxis, or when diagnosing patients with *hymenoptera venom* allergy, mastocytosis symptoms, or certain haematologic malignancies. It's worth noting that nearly 80% of people with the HαT trait have BST levels surpassing the upper limit of normal cited by most laboratories, which is 11.4 ng/mL.

Tryptase genotyping is necessary to confirm the trait. A droplet digital polymerase chain reaction (ddPCR) assay is employed to demonstrate an increased copy number of the *TPSAB1* gene responsible for encoding alpha-tryptase [39, 40]. It's important to mention that routine next-generation sequencing methods may not be sufficient for characterizing tryptase gene composition or copy numbers accurately [41].

In highly symptomatic individuals, further evaluation becomes crucial. While HαT is a common condition and many patients may exhibit minimal or no symptoms, it's important to consider the possibility of coexisting disorders in those experiencing pronounced symptoms. This includes individuals displaying signs and symptoms suggestive of mastocytosis, MCAS or clonal myeloid diseases such as lymphadenopathy, hepatosplenomegaly, abnormalities in complete blood count, eosinophilic tissue infiltration, anaphylaxis (particularly hypotensive), cutaneous symptoms of mastocytosis and the presence of Darier's sign [42, 43].

To diagnose MCAS, which can present similar clinical features, three criteria must be met [7, 44]: (a) documented evidence of typical clinical symptoms that result from recurrent acute systemic MCA, resembling episodes of recurrent anaphylaxis (b) a significant and temporary increase in MC-derived mediators (e.g., tryptase, histamine, and prostaglandin D2 metabolites) in serum and urine, which should be compared to baseline levels measured before the event or at least 24 hours after all clinical signs and symptoms have completely subsided, and (c) positive response to drugs that block MCA or inhibit MC mediators, production, or effects [7].

TREATMENT STRATEGIES OF HαT AND FAMILIAL/HEREDITARY MCAS

Pharmacotherapy is the primary approach for treating symptomatic individuals with HαT, which is similar to the treatment used for clonal mast cell disorders. The treatment involves various medications such as H1- and H2-antihistamines, MC stabilizers like compounded oral ketotifen or cromolyn sodium, leukotriene modifiers, and, in some cases, aspirin or intermittent courses of oral corticosteroids [22].

Patients experiencing anaphylaxis should have at least two epinephrine autoinjectors and should be educated on their proper use.

In retrospective studies, omalizumab was found to improve cutaneous and respiratory symptoms connected with MCA [28, 45]. In a trial, described by Carter et al. [27], one individual with HαT who received omalizumab experienced a reduction in anaphylaxis episodes compared to one patient who received a placebo [27]. Moreover, a retrospective study conducted by Giannetti et al. [45], also reported a decrease in anaphylaxis episodes among HαT patients treated with omalizumab.

It is really important to monitor symptomatic individuals with HαT for bone loss, for the following reasons. Firstly, many clinical reports, have connected high BST levels with premature osteopenia and osteoporosis. Secondly, increased populations of bone marrow MCs and eosinophils have been observed in symptomatic individuals with HαT which may be a risk factor for early onset of bone loss. Lastly, symptomatic individuals with HαT often receive high-dose systemic corticosteroids, which can contribute to bone loss. Therefore, it is recommended to perform bone densitometry in symptomatic adult patients (both male and female) [30, 46].

Conclusions

In summary, HαT is a genetic condition characterized by an increased number of copies of the *TPSAB1* gene, which encodes for alpha-tryptase.

HαT may manifest with a diverse range of clinical symptoms including immediate hypersensitivity reactions, allergies, pruritus (itching), flushing, joint hypermobility, connective tissue disorders, and functional gastrointestinal diseases. However, approximately two-thirds of individuals with HαT show minimal or no symptoms.

Importantly, individuals with HαT are at an increased risk of developing anaphylaxis, particularly when they have coexisting IgE-dependent allergies or systemic mastocytosis. Currently, HαT is considered a heritable modifier of both idiopathic and *Hymenoptera venom anaphylaxis* [1].

A specific subtype of MCAS, known as hereditary/familial MCAS or HαT + MCAS, has been identified in association with HαT.

Further research is needed to delve deeper into the relationship between HαT and MCAS to determine whether MCAS exists independently of HαT or not. These investigations aim to enhance our understanding of these conditions and improve diagnostic and treatment approaches.

Article information and declarations

Author contributions

The authors confirm their contribution to the paper as follows: study conception and design: Rydz Agnieszka, Lange Magdalena; data collection: Rydz A, Lange M; analysis and interpretation of results: Rydz A, Lange M; draft manuscript preparation: Rydz A, Lange M All authors approved the final version of the manuscript.

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Conflict of interest

The authors of this publication declare no conflicts of interest.

Supplementary material

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