Hereditary Alpha Tryptasemia

Genotyping and Associated Clinical Features

Jonathan J. Lyons, MD

KEYWORDS

• Mast cell activation • Hypertryptasemia • Autosomal dominant • Genotyping

KEY POINTS

- Hereditary alpha tryptasemia is a genetic trait that leads to elevated basal serum tryptase.
- Some individuals with hereditary alpha tryptasemia present with a syndrome comprised of multisystem complaints.
- Increased *TPSAB1* copy number encoding alpha-tryptase on a single allele is the cause of hereditary alpha tryptasemia.
- A gene-dosage effect exists between number of additional *TPSAB1* copies, basal serum tryptase levels, and severity of clinical symptoms in affected individuals.
- Complex structural variation at the tryptase locus prevents identification of increased *TPSAB1* copy number by conventional exome or genome sequencing.

INTRODUCTION

Tryptase is a protein expressed by mast cells and basophils.[1,2] Mature, enzymatically active tryptases are tetrameric serine proteases that are stored in mast cell secretory granules and contribute to allergic inflammation.[3] Experiments inhibiting mature tryptases have demonstrated their role in promoting inflammatory cell recruitment, vascular permeability, and airway hypersensitivity and remodeling, in animal models. However, the specific contribution of mature tryptases to allergic reactions in humans is less clear.[4] Pro-tryptases, which have not undergone enzymatic conversion into mature tetrameric tryptases, are constitutively secreted into serum in their monomeric form, and provide the vast majority of measured basal serum tryptase (BST) in healthy individuals[5,6] (**Fig. 1**). Pro-tryptases are also the predominant forms of tryptase

Disclosure Statement: The author declares no competing or conflicting interests.
Funding: This research was supported by the Division of Intramural Research of the National Institute of Allergy and Infectious Diseases, NIH.
Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 10, Room 11N240 MSC 1889, 10 Center Drive, Bethesda, MD 20892, USA
E-mail address: jonathan.lyons@nih.gov

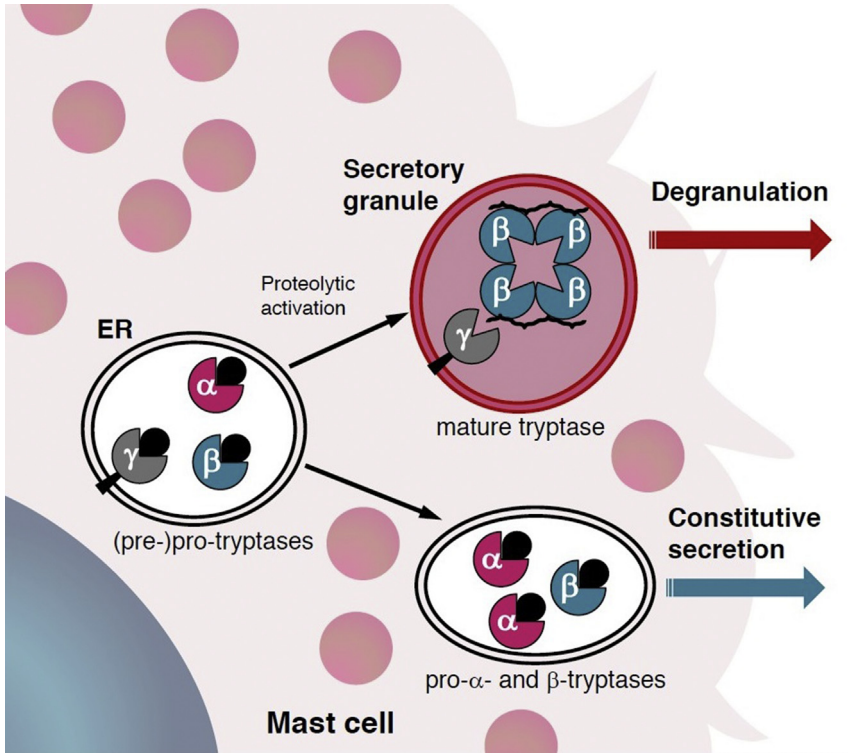

Fig. 1. Schematic of tryptase secretion from human mast cells. Pro-tryptases generated in mast cells undergo sequential proteolytic cleavage to become mature tetrameric tryptase, stabilized by heparin, and stored in secretory granules (*top*) awaiting appropriate stimuli to induce degranulation. Alternatively, pro-tryptases can be secreted constitutively into serum as enzymatically inactive pro-peptides (*bottom*). ER, endoplasmic reticulum. (*Adapted from* Caughey GH. Tryptase genetics and anaphylaxis. J Allergy Clin Immunol 2006;117(6):1412; with permission.)

present in the serum from patients with systemic mastocytosis.[7,8] During mast cell degranulation, as occurs during immunoglobulin (Ig)E-mediated immediate hypersensitivity reactions, mature tryptases are released with other mast cell mediators and contribute to symptoms of type I allergic reactions. Thus, serum tryptase in this setting is a useful biomarker for the clinical diagnosis of anaphylaxis.[9]

However, elevated BST, currently defined clinically as >11.4 ng/mL, appears to be quite common, being reported in 4% to 6% of the general population.[10,11] Although in some individuals reported increases may be due to end-stage renal disease or clonal expansion of myeloid or mast cells, including mastocytosis,[12–14] it has recently been discovered that a number of individuals with elevated BST inherit this trait.[15–18] Further, in the small cohorts studied thus far, the data suggest that this trait may also be relatively common, and frequently the cause for elevated BST in the general population.[16,18] The focus of this review is to discuss the details of this genetic trait and the complexities surrounding genotyping patients, as well as the associated clinical features and management approaches for patients with the multisystem complaints associated with hereditary alpha tryptasemia.