# Interpreting an elevated tryptase

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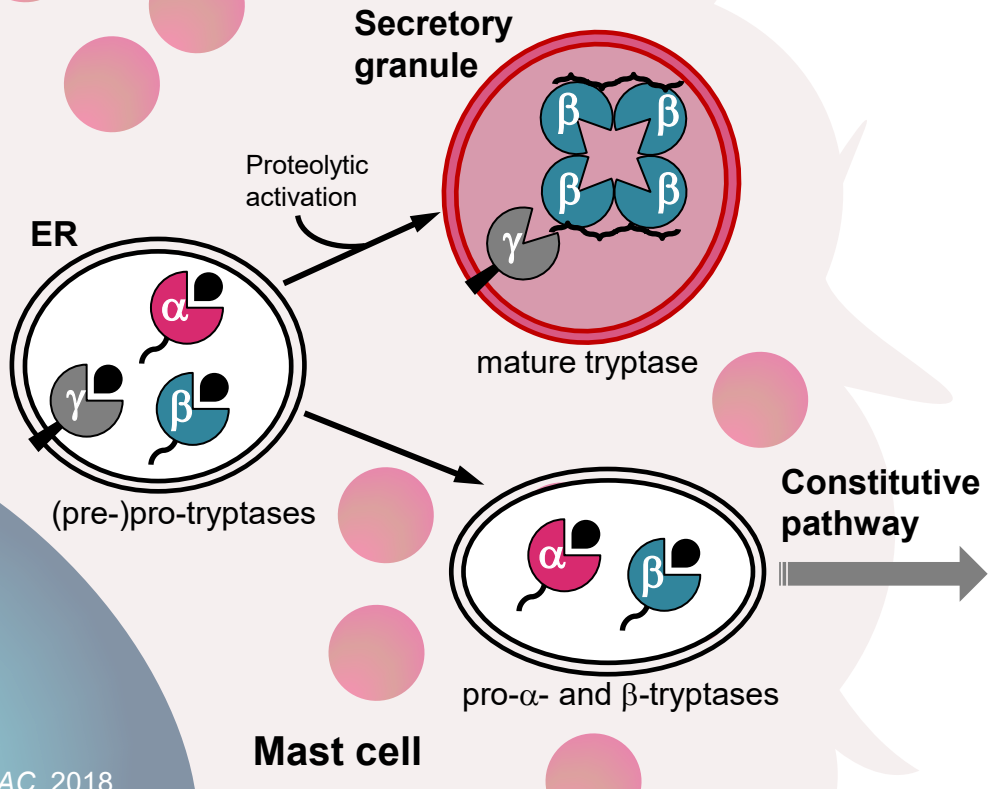
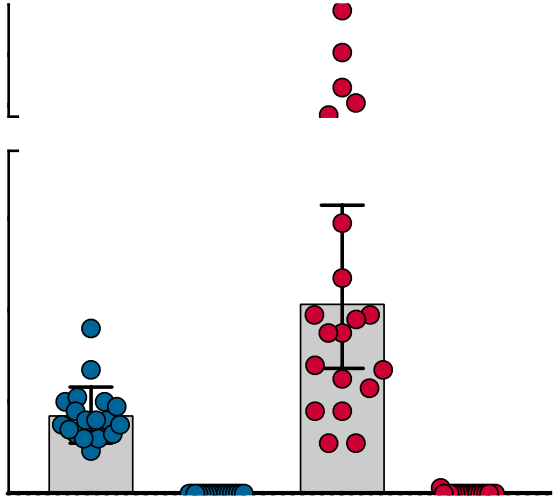
# Learning Objectives

- Describe the genetic basis for hereditary alpha-tryptasemia (HαT)
- Identify the clinical significance of elevated baseline serum tryptase in the absence of HαT
- Recognize that BST levels are labile and impact the correct interpretation of this biomarker
- Understand the association between HαT and mast cell disorders and its impact on diagnosis of these conditions

# Basal serum tryptase (BST) is comprised of enzymatically inactive pro-tryptases



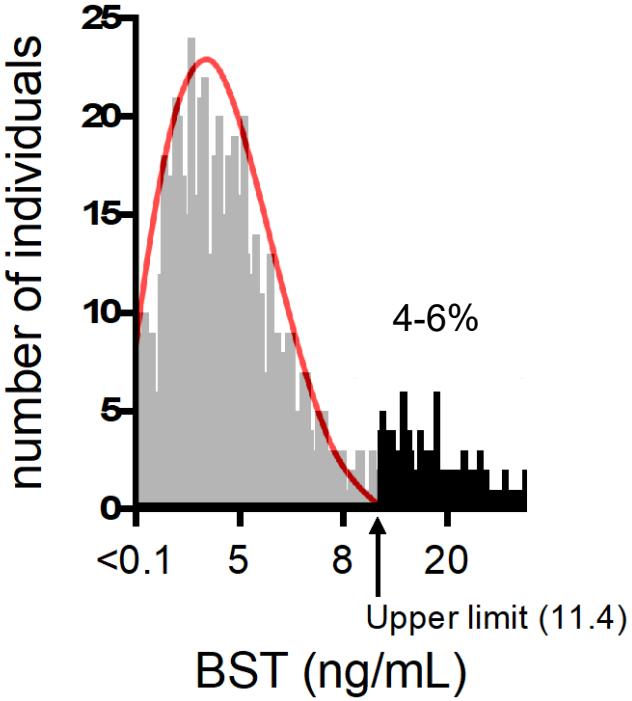



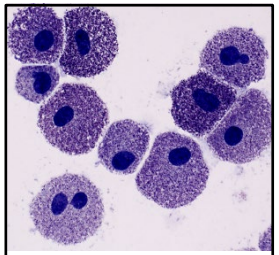
Non-clonal
ISM

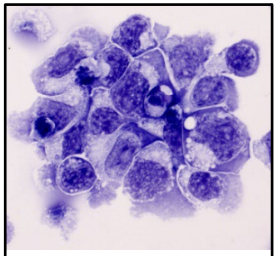
Mateja et al., Lyons. *JACI*. 2021

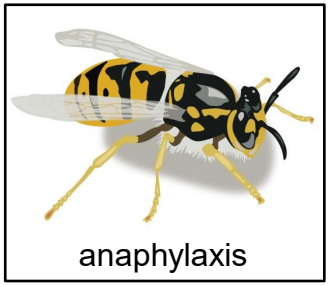
Lyons. *IAC*. 2018

# Elevated pro-tryptase is common and associated with clonal myeloid neoplasms and severe anaphylaxis





mast cell diseases


myeloproliferative diseases


anaphylaxis

Lyons et al. *JACI.* 2014
Khoury & Lyons. *Curr Allergy Asthma Rep.* 2019

Desai et al., Lyons. *JACI.* 2019

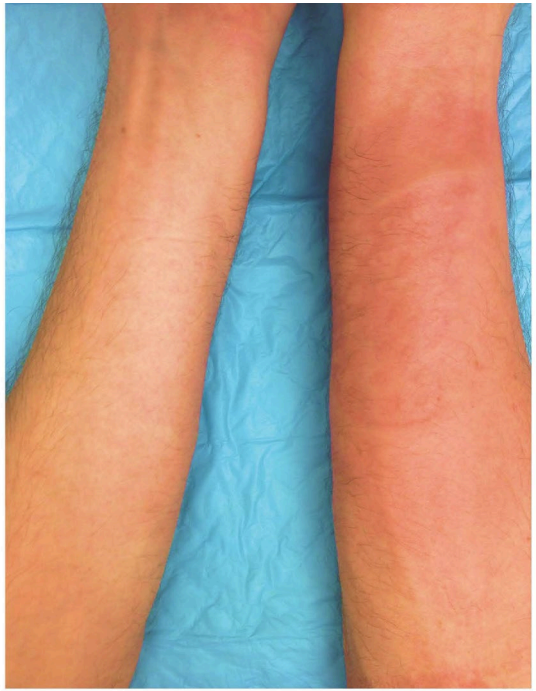
# Elevated BST is associated with skin & GI symptoms and systemic immediate hypersensitivity

| | serum tryptase (ng/mL) >11.4 | <11.4 | P-value |
|---|---|---|---|
| *Frequency of symptoms* | | | |
| Fatigue | 56% | 37% | <0.01 |
| Meteorism[b] | 42% | 15% | <0.0001 |
| Headache | 37% | 38% | n.s. |
| Muscle and bone ache | 36% | 16% | <0.001 |
| Swinging mood | 36% | 19% | <0.01 |
| Vertigo | 31% | 8% | <0.0001 |
| Tachycardia | 29% | 10% | <0.001 |
| Flush | 25% | 7% | <0.001 |
| Acid reflux | 24% | 15% | n.s. |
| Palpitations | 23% | 8% | <0.01 |
| Pruritus | 22% | 18% | n.s. |
| Diarrhoea[b] | 22% | 8% | <0.01 |
| Hypotension | 18% | 7% | <0.05 |
| Abdominal pain[b] | 18% | 7% | <0.01 |
| Angio-oedema | 15% | 2% | <0.01 |

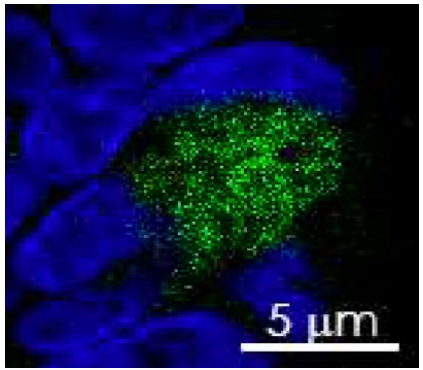
- Cutaneous symptoms
- GI complaints
- Systemic MC-mediated symptoms

Fellinger et al. *Allergol Immunopathol.* 2014

# Clinical features among families referred to NIH with elevated basal serum tryptase



- Systemic MC-mediated reactions
  - Venom and foods
- Cutaneous symptoms
  - Flushing/pruritus
  - Associated sleep disruption
- Specific CT abnormalities
  - Retained primary dentition
  - Associated chronic pain
- “Functional” GI disorders
  - Dysphagia
  - IBS-like symptoms
  - Chronic reflux symptoms

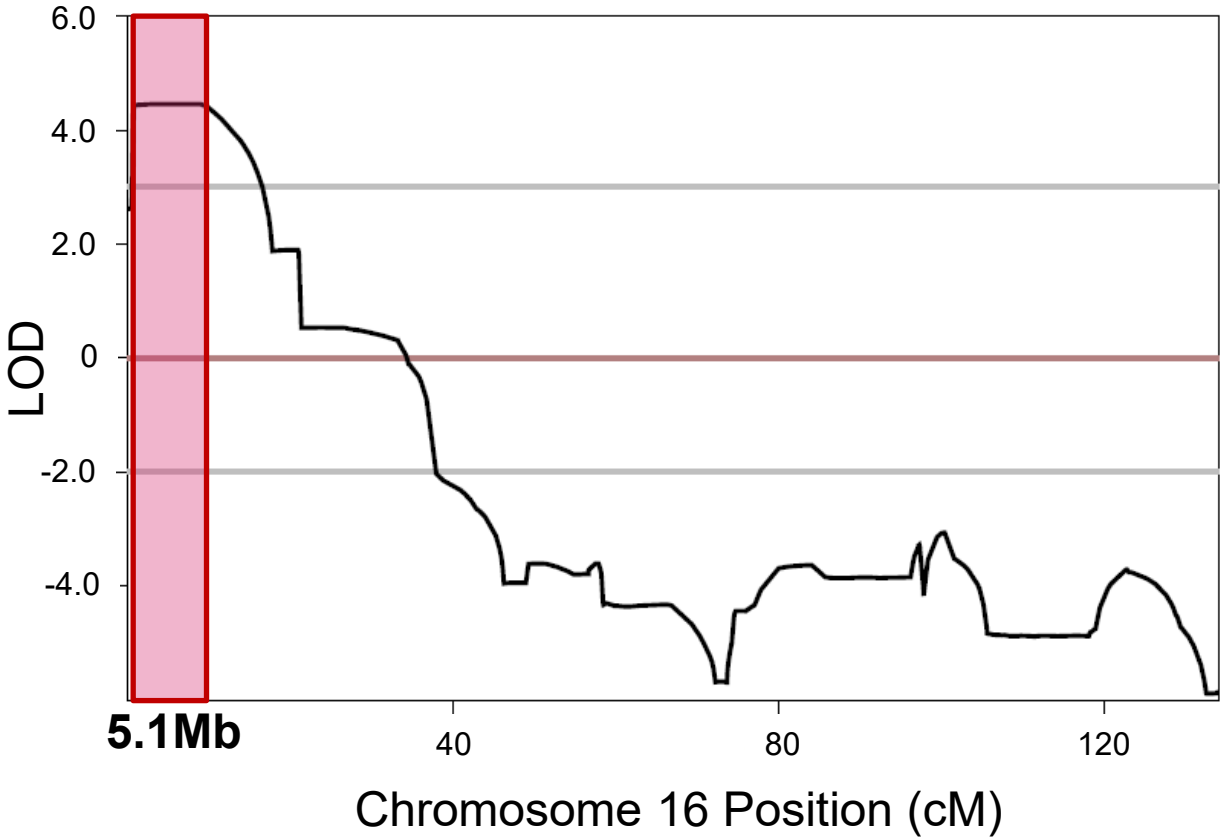



Enhanced Caspase-1 activation

Lyons et al. *J. Allergy Clin. Immunol.* 2014

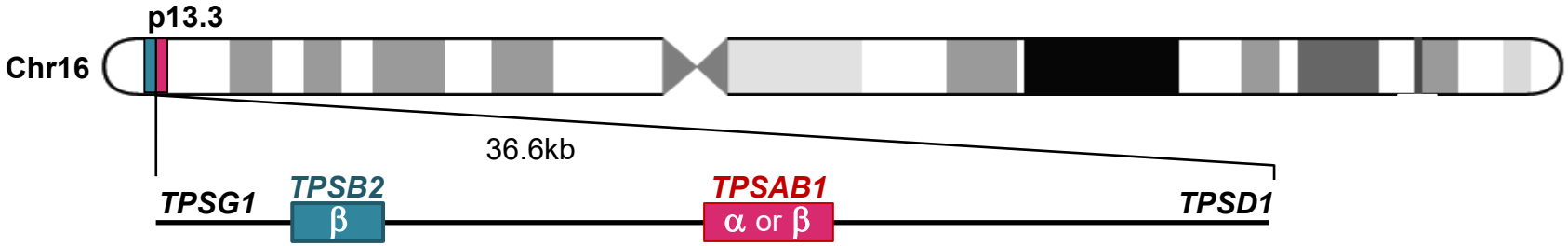
Konnikova et al., Lyons. *JACI.* 2021

# Elevated basal serum tryptase links to 16p13.3




Lyons et al. *Nat Genet.* 2016

# Hereditary α-tryptasemia: genetic trait caused by *TPSAB1* replications

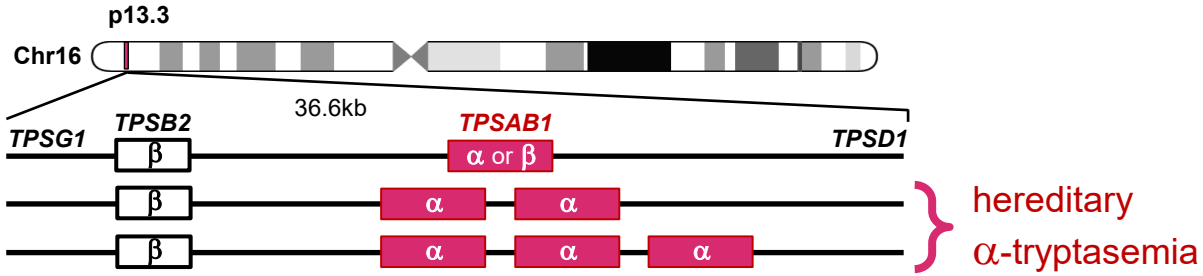


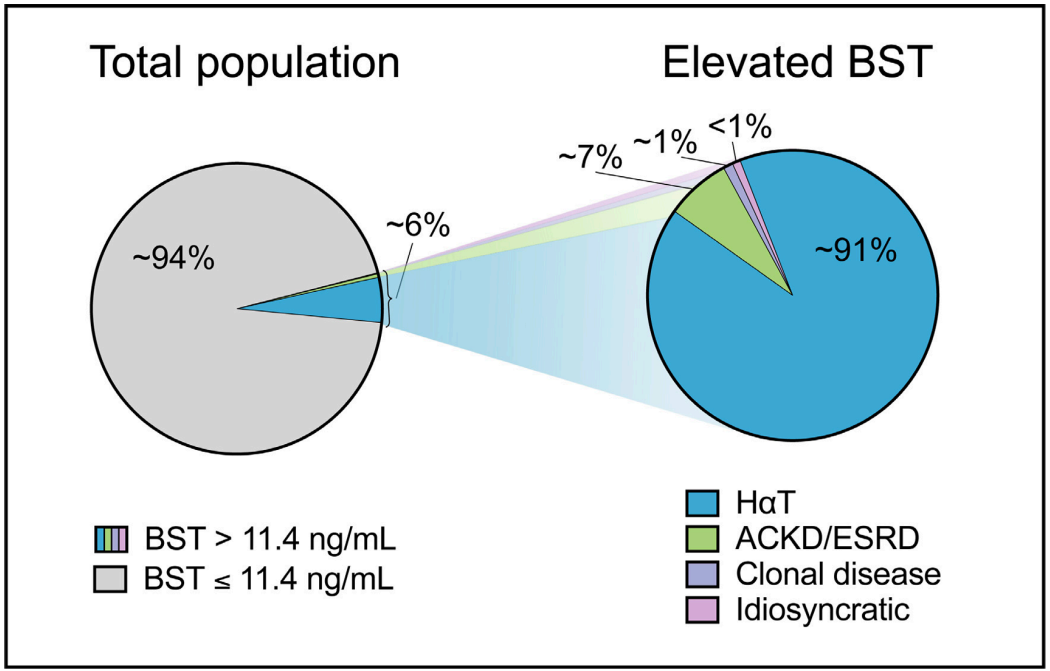

## Canonical tryptase genotypes

| | |
|---|---|
| β/β, β/β = 4β:0α | 30% |
| α/β, β/β = 3β:1α | 44% |
| α/β, α/β = 2β:2α | 21% |

Lyons et al. *Nat Genet.* 2016

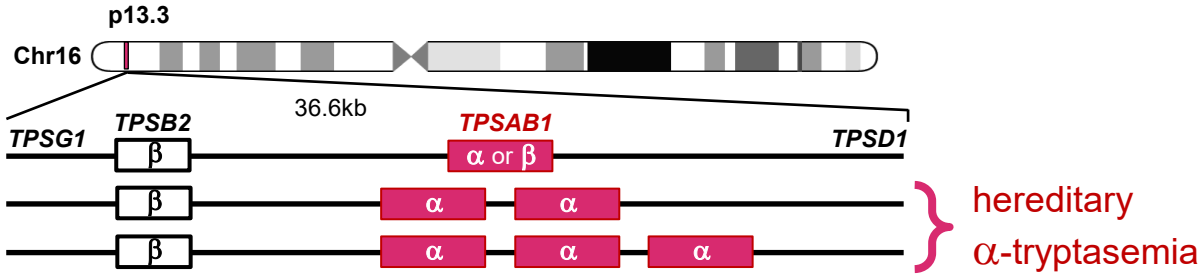
Lyons et al. *Nat Genet.* 2016

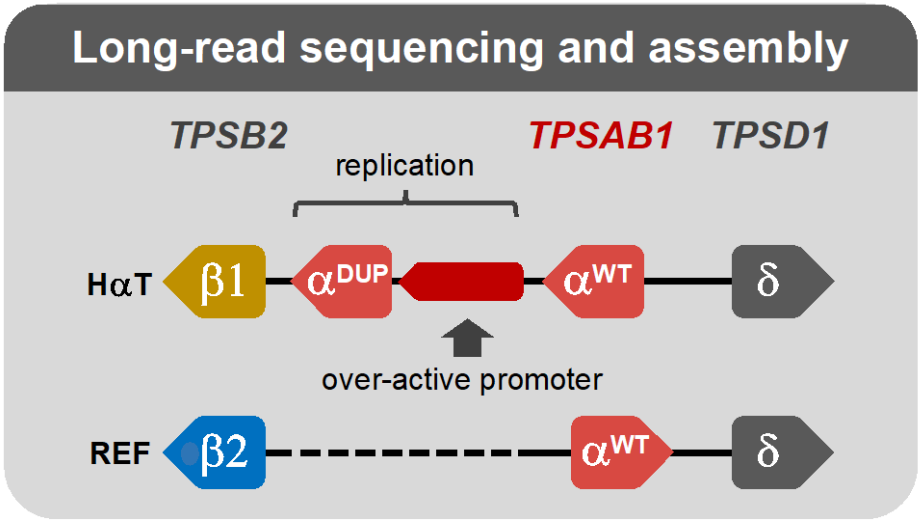


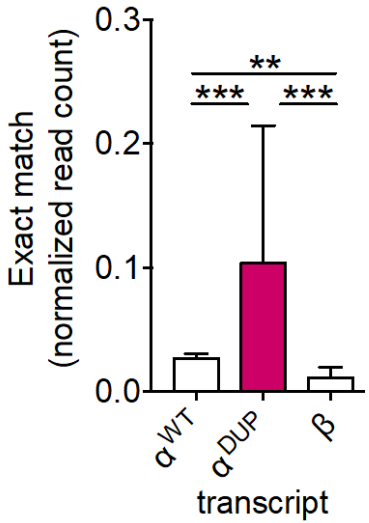



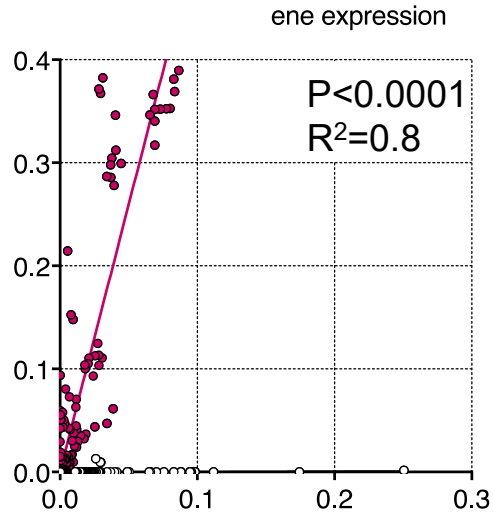

Lyons. *Ann Allergy Asthma Immunol.* 2021

Lyons et al. *Nat Genet.* 2016



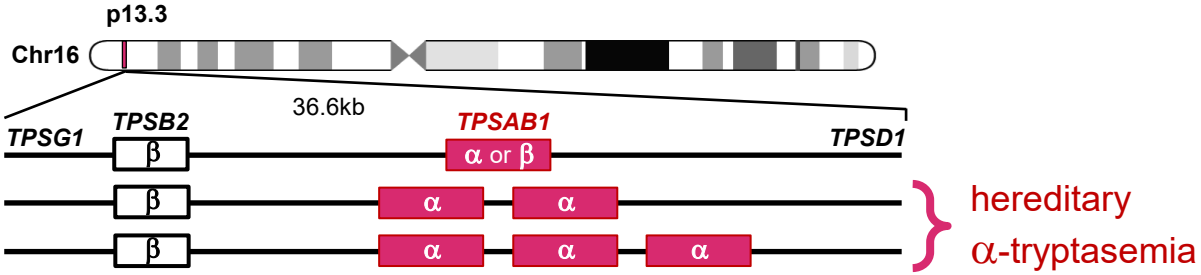



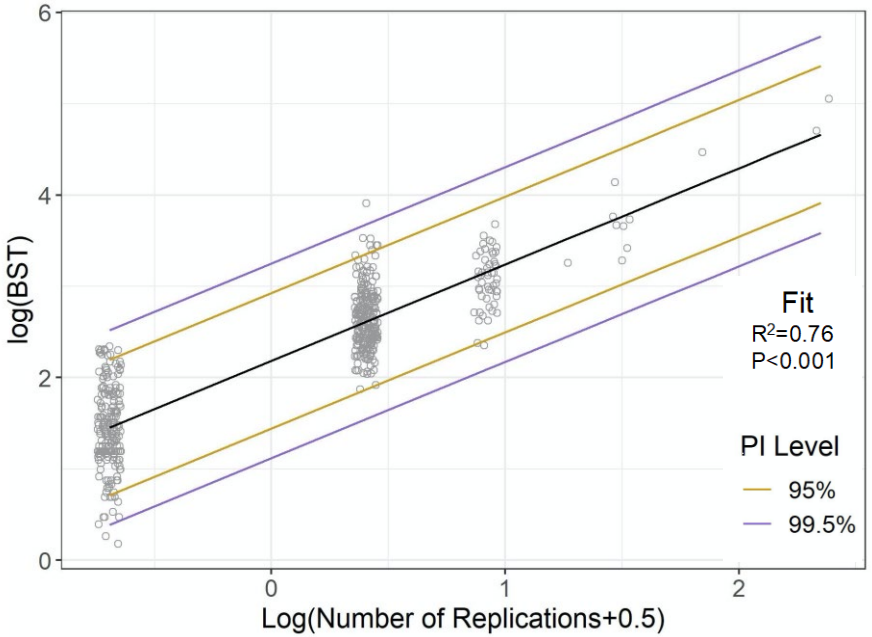




Chovanec et al., Lyons. *Blood Adv*. 2022

Lyons et al. *Nat Genet.* 2016




## Redefine reference ranges

| *TPSAB1* replication (N) | BST median level (ng/mL) | BST upper limit (ng/mL) |
|---|---|---|
| 0 | 4.2 | 11.4 |
| 1 | 13.6 | 36.2 |
| 2 | 23.4 | 62.2 |
| 3 | 33.3 | 88.8 |
| 4 | 43.4 | 115.9 |

Chovanec et al., Lyons. *Blood Adv*. 2022

Lyons et al. *Nat Genet.* 2016

# HαT impacts the specificity of using BST as a minor clinical criterion for diagnosing systemic mastocytosis

**Table 3.3** WHO diagnostic criteria for systemic mastocytosis[a]

| |
|---|
| *Major criterion* |
| Multifocal dense aggregates of mast cells (≥15/HPF) in bone marrow or extracutaneous sections |
| *Minor criteria* |
| >25% of the mast cells are spindle-shaped, atypical, or immature in morphology |
| *KIT* p.D816V or other *KIT* GOF mutation present. |
| Aberrant expression of CD2 and/or CD25[b] |
| Total serum tryptase >20 ng/mL[b] |

[a]One major and one minor or three minor criteria must be met for diagnosis

[b]Invalid when another clonal myeloid disorder is present

Lyons & Schwartz. *Mastocytosis*. 2019

# *The upper limit of 'normal' for BST levels is determined by the number of TPSAB1 replications*

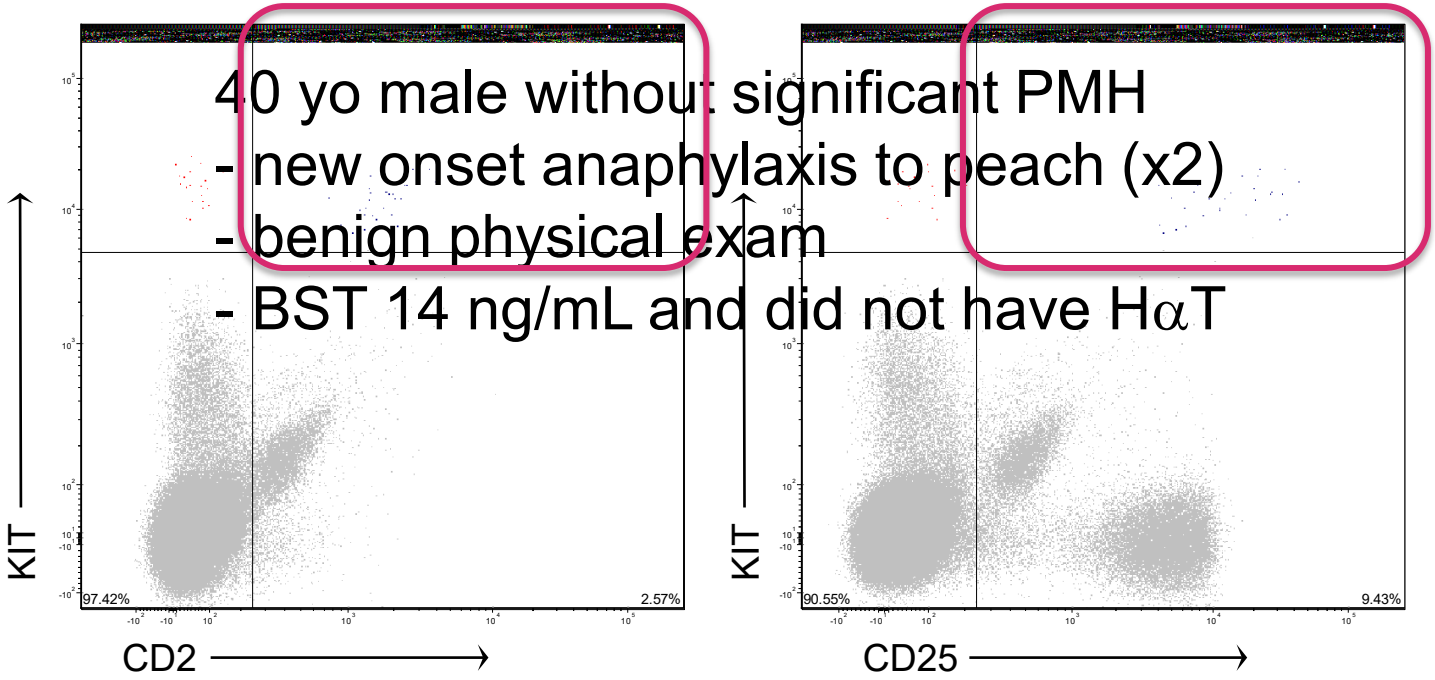
| *TPSAB1* replication number | 0 | 1 | 2 | 3 | 4 | 6 | 10 |
|---|---|---|---|---|---|---|---|
| BST (ng/mL) | 4.1 | 13.6 | 22.5 | 27.3 | 37 | 87 | 133 |
| Upper limit: 99.5% PI for BST | 11.4 | 36.2 | 62.2 | 88.8 | 115.9 | 171.2 | 285.1 |
| Upper limit: BST/(1+replication #) | 20 | 40 | 60 | 80 | 100 | 140 | 220 |

Lyons et al. *JACI Pract.* 2022

*start at 40ng/mL upper limit for anyone with HαT and add 20ng/mL for every copy more than 1

# Elevated BST in the absence of HαT identifies clonal mast cell disease

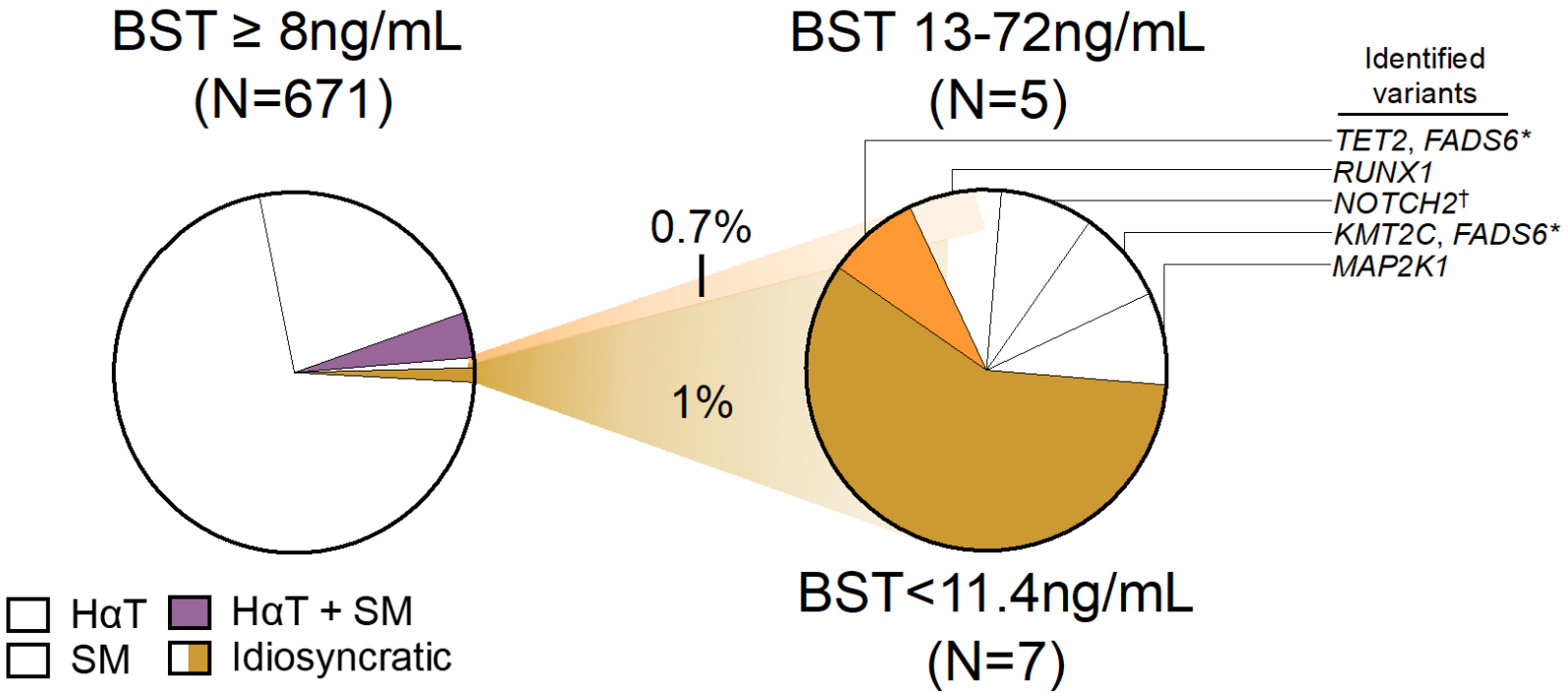
40 yo male without significant PMH
- new onset anaphylaxis to peach (x2)
- benign physical exam
- BST 14 ng/mL and did not have HαT




*KIT* p.D816V positive

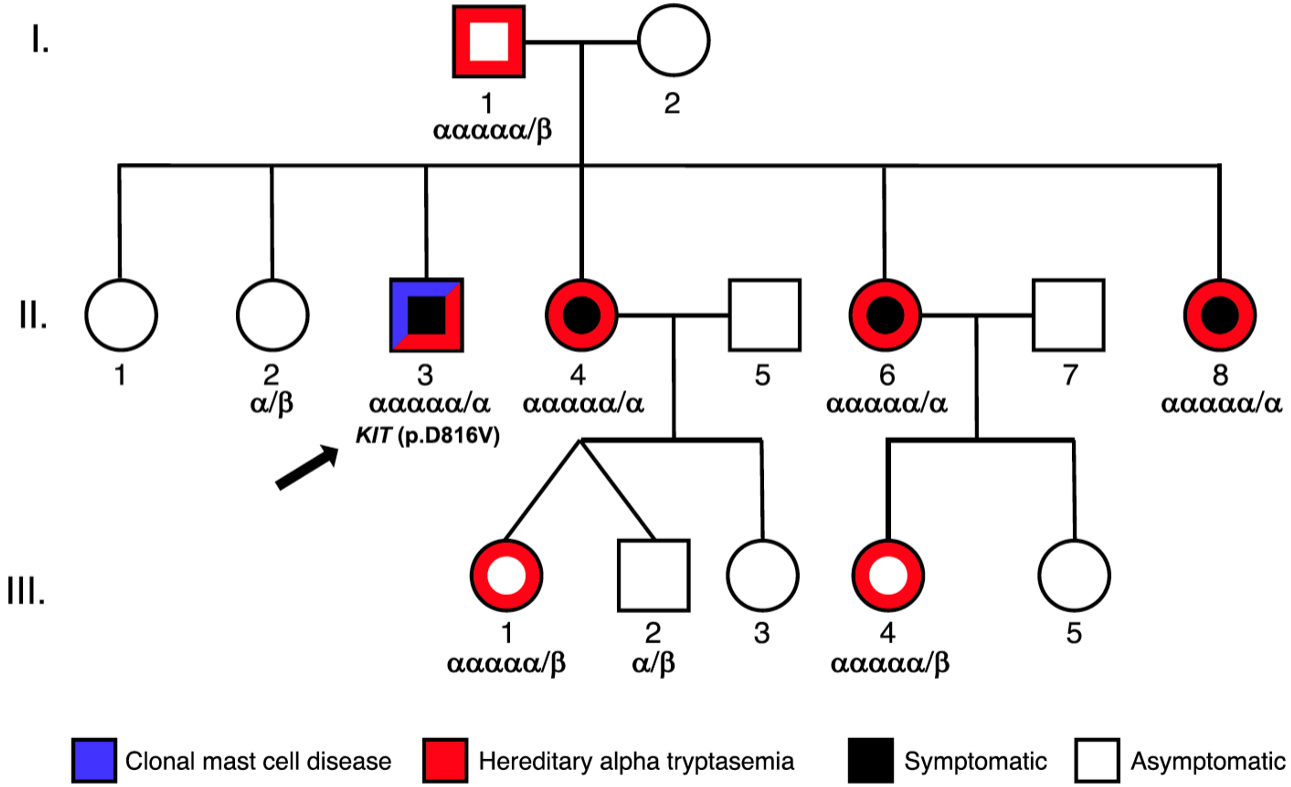
Prior diagnosis = MMAS **NOW = ISM**

# Elevated BST in the absence of HαT identifies indolent or evolving clonal myeloid hematopoiesis



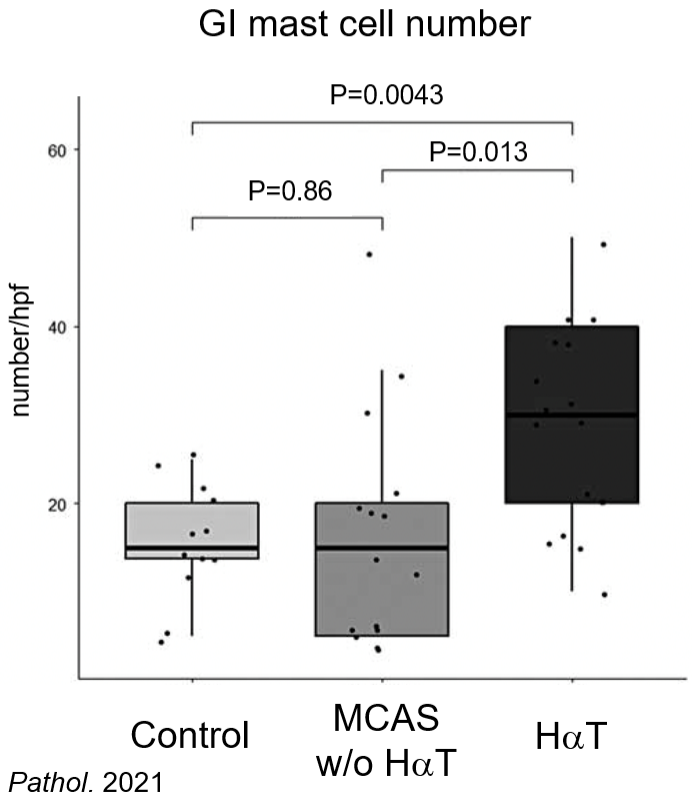

Chovanec et al., Lyons. *Blood Adv*. 2022

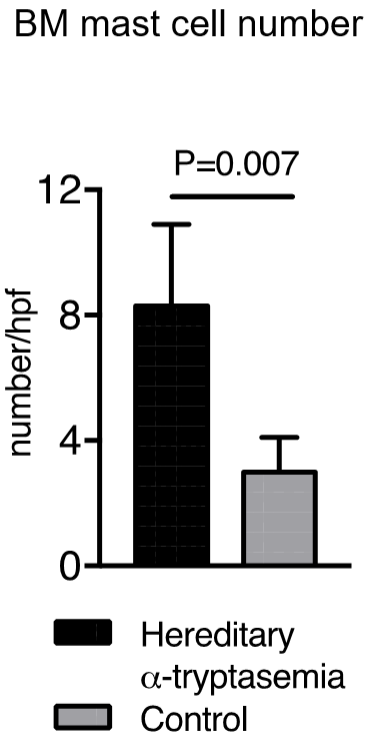
# A rare clone and a rare HαT-associated genotype: happenstance or harbinger?




Sabato et al., Lyons. *J Clin Immunol*. 2018

# HαT is associated with increased mast cells in the bone marrow and GI mucosae

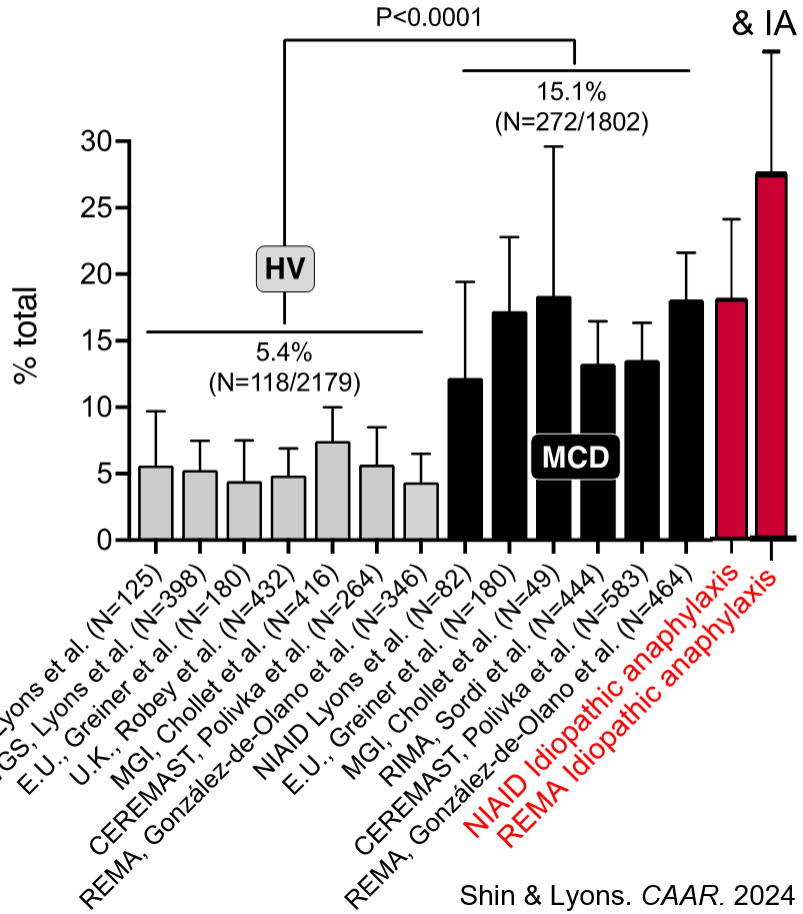


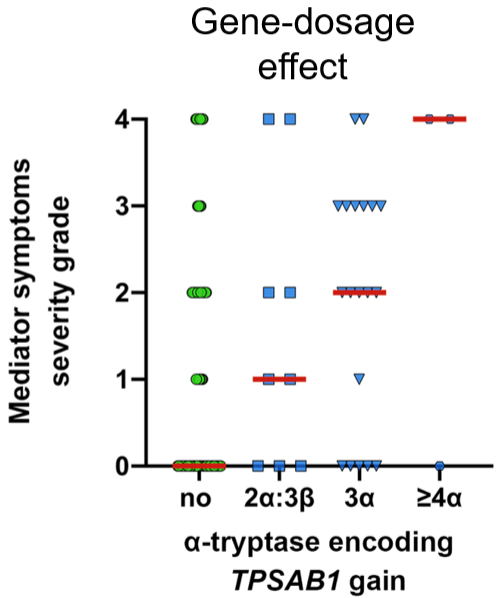

Hamilton et al. *Am J Surg Pathol.* 2021
Konnikova et al., Lyons. *JACI.* 2021

Lyons et al. *JACI.* 2014
Giannetti et al. *JACI.* 2021

# HαT is associated with clonal mast cell disease (MCD) and more severe symptoms

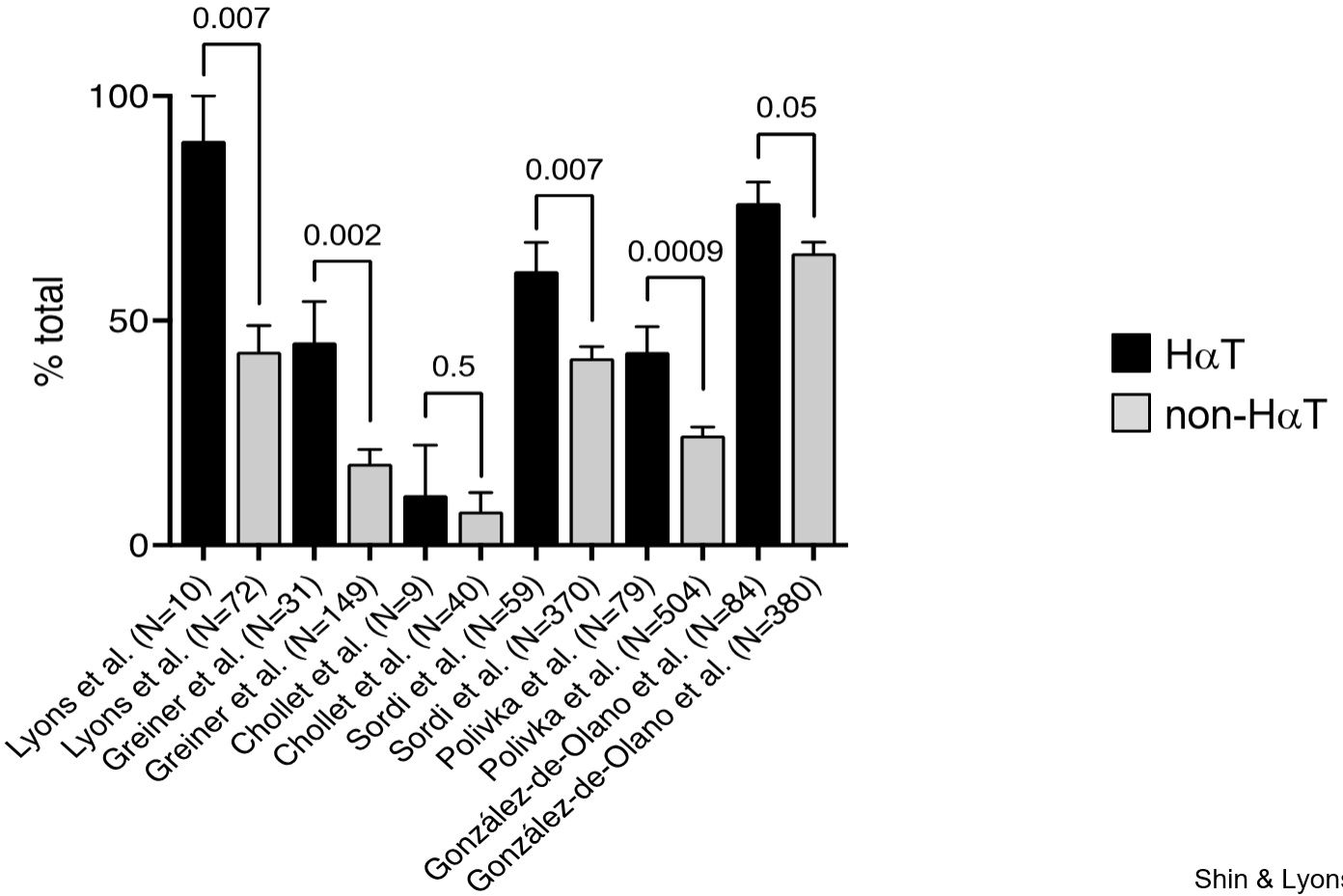



Shin & Lyons. *CAAR*. 2024



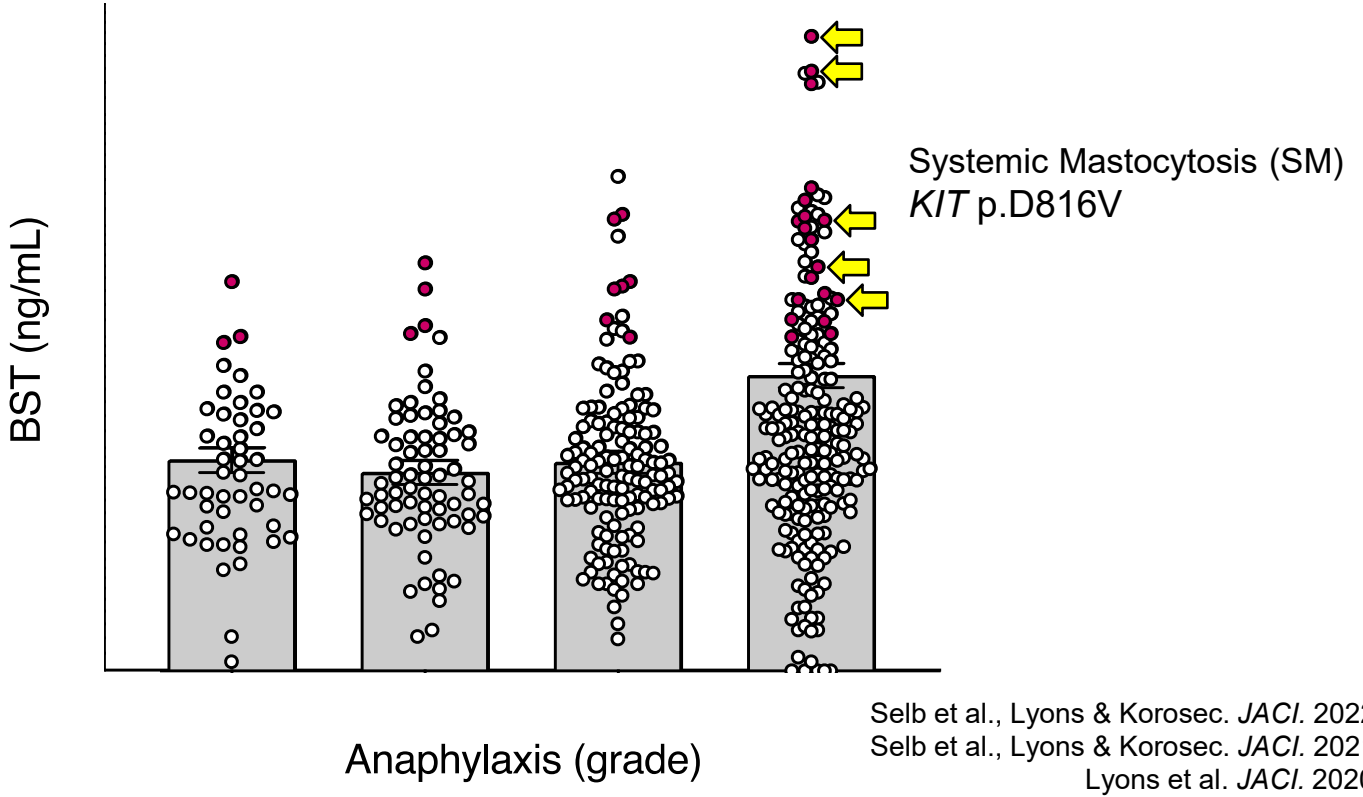

Greiner et al. *Blood*. 2020

# HαT is associated with anaphylaxis risk in MCD patients




Shin & Lyons. *CAAR.* 2024

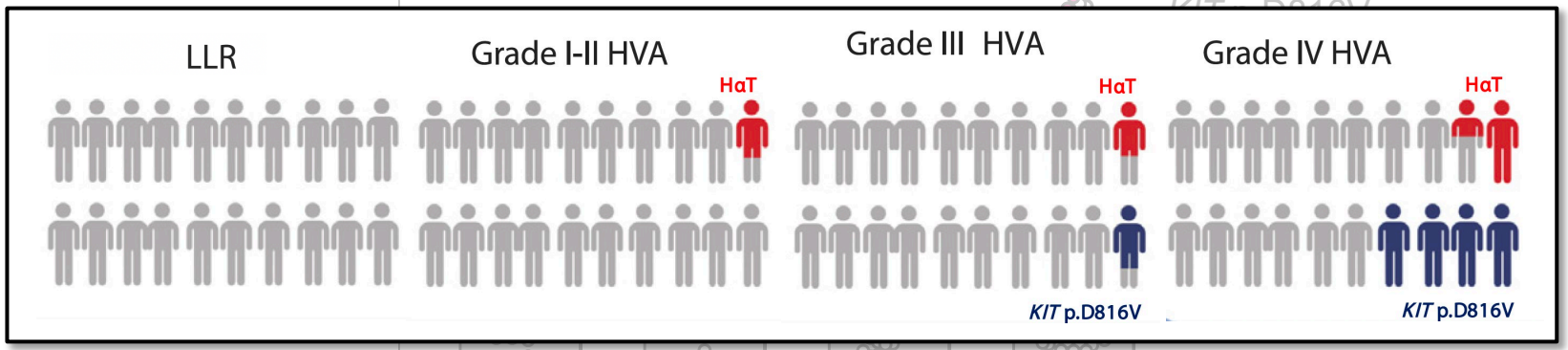
# HαT is associated with severe Hymenoptera venom anaphylaxis




Selb et al., Lyons & Korosec. *JACI.* 2022
Selb et al., Lyons & Korosec. *JACI.* 2021
Lyons et al. *JACI.* 2020

# HαT is associated with severe Hymenoptera venom anaphylaxis

N=881, OR=2.2, P=0.006

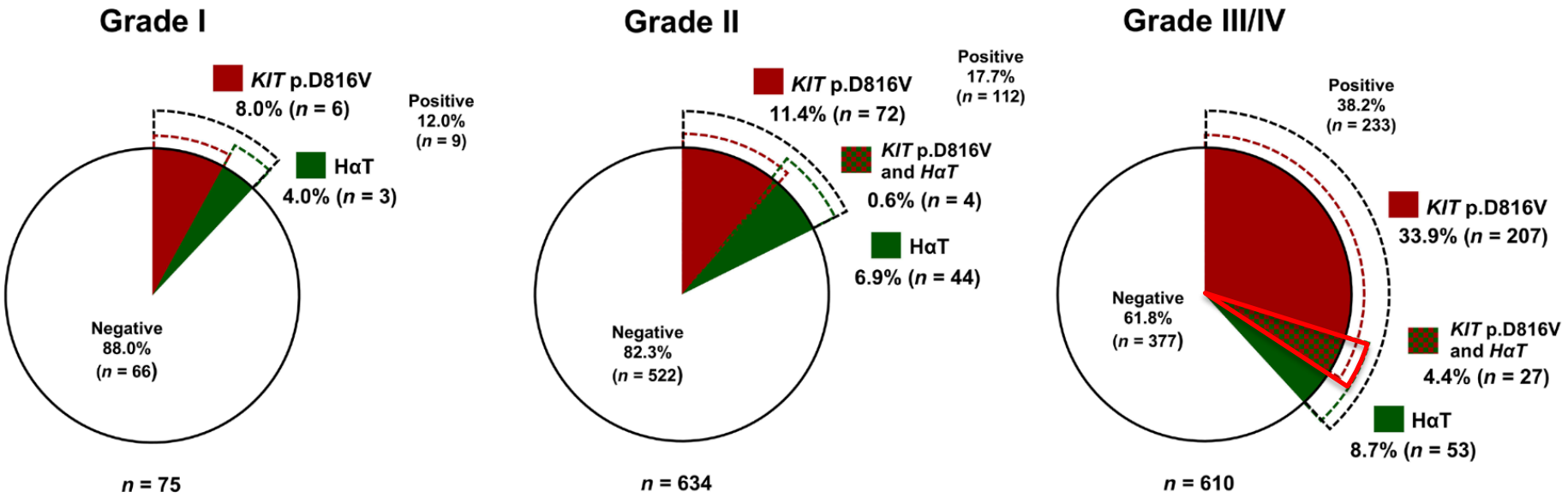



Systemic Mastocytosis (SM)

Anaphylaxis (grade)

Selb et al., Lyons & Korosec. *JACI.* 2022
Selb et al., Lyons & Korosec. *JACI.* 2021
Lyons et al. *JACI.* 2020

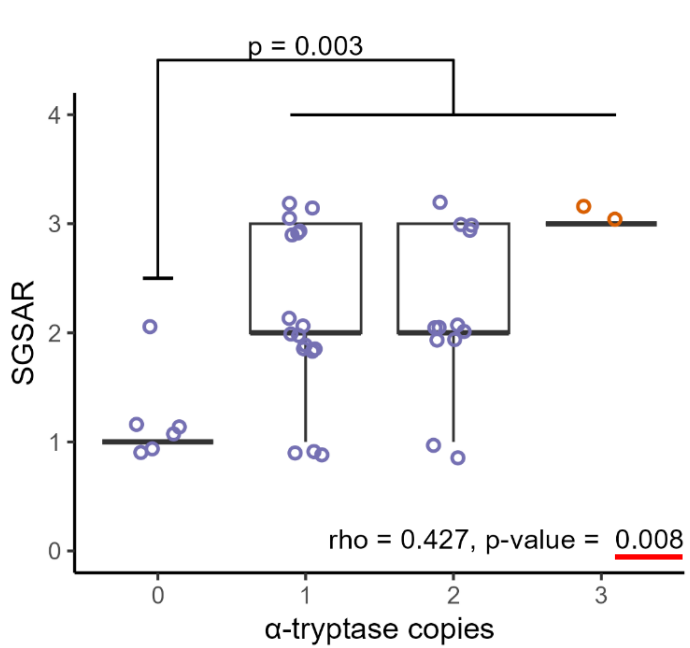
# Hereditary α-tryptasemia: risk factor for severe venom anaphylaxis

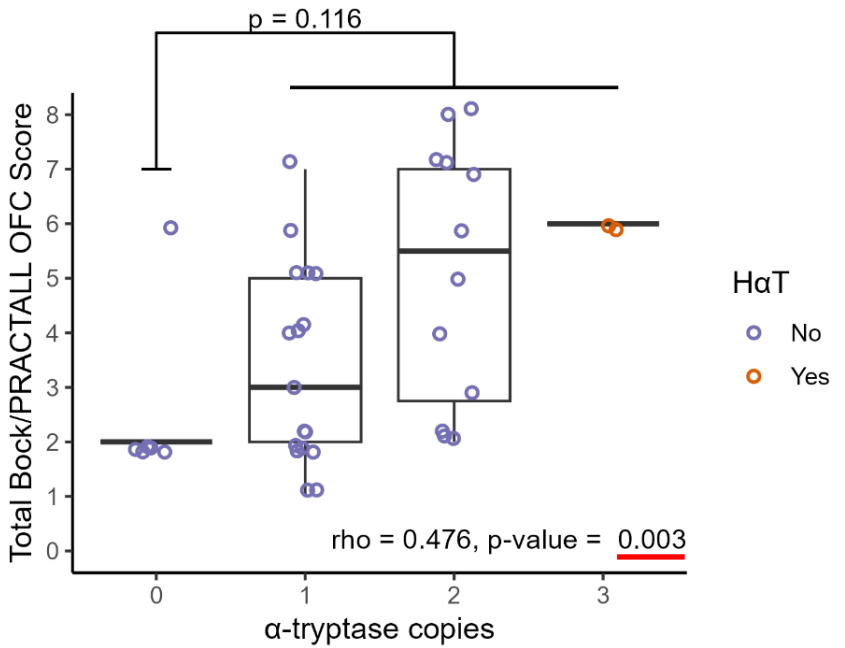



87% (27/31) with HαT and *KIT* p.D816V had Grade III/IV anaphylaxis

Korošec et al. *Allergy*. 2024

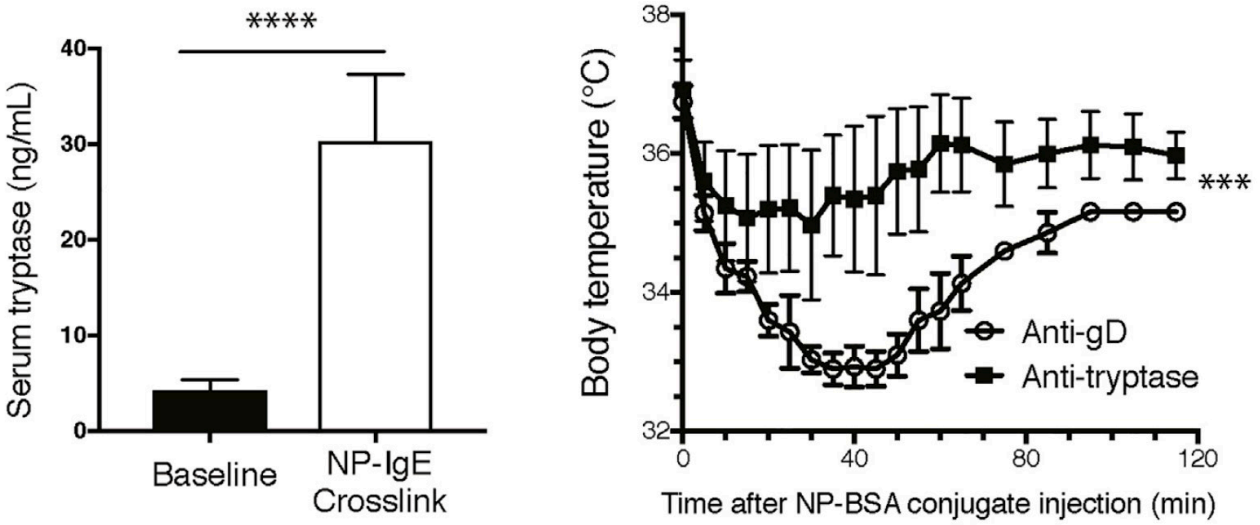
# α-Tryptase is associated with more severe food reactions



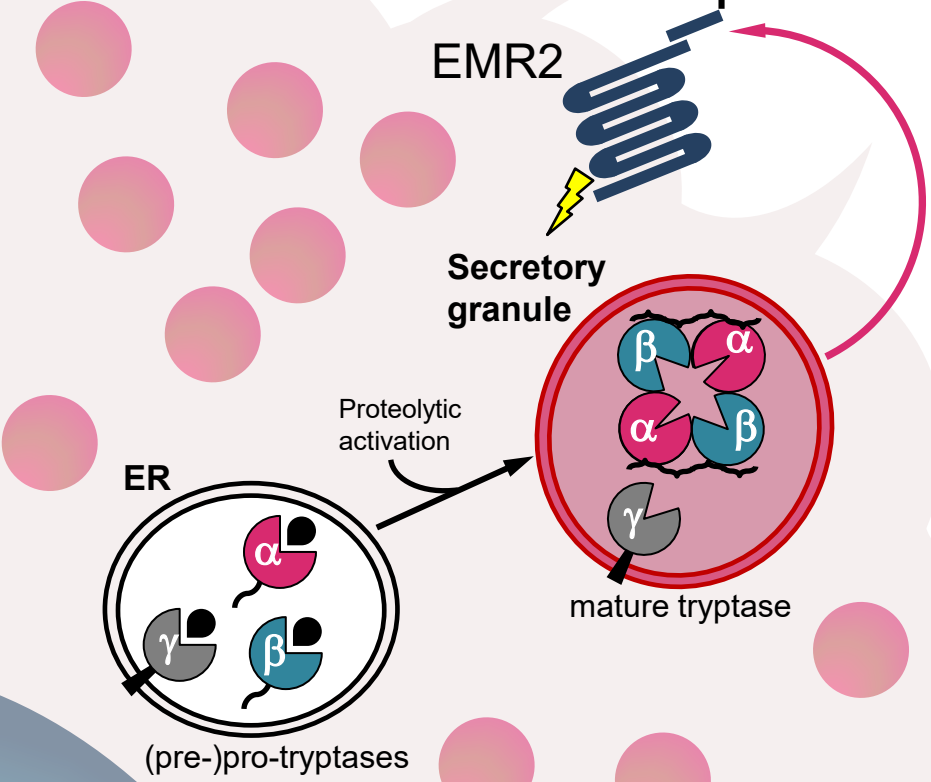

Lang et al., Lyons. *JACI.* 2023

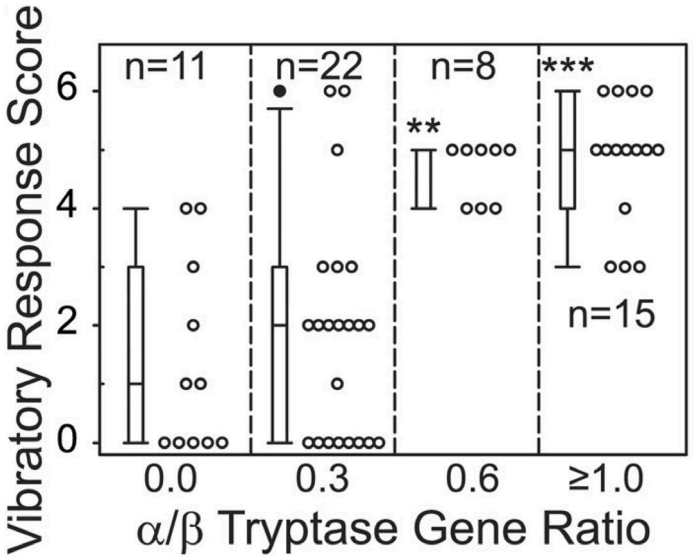
# Tryptase neutralization reduces anaphylaxis severity in a humanized mouse model




Maun et al. *Cell.* 2019

# α/β-Heterotetrameric tryptases cleave EMR2 to promote vibratory symptoms

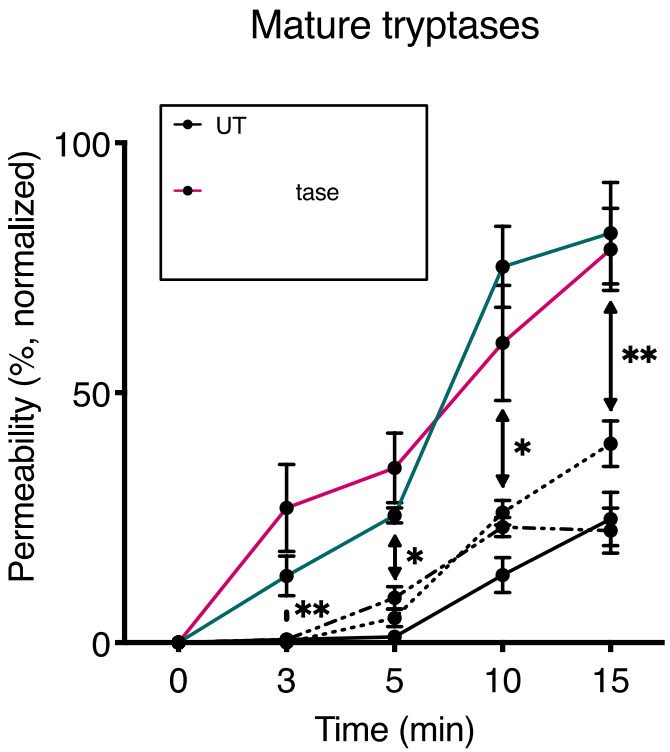


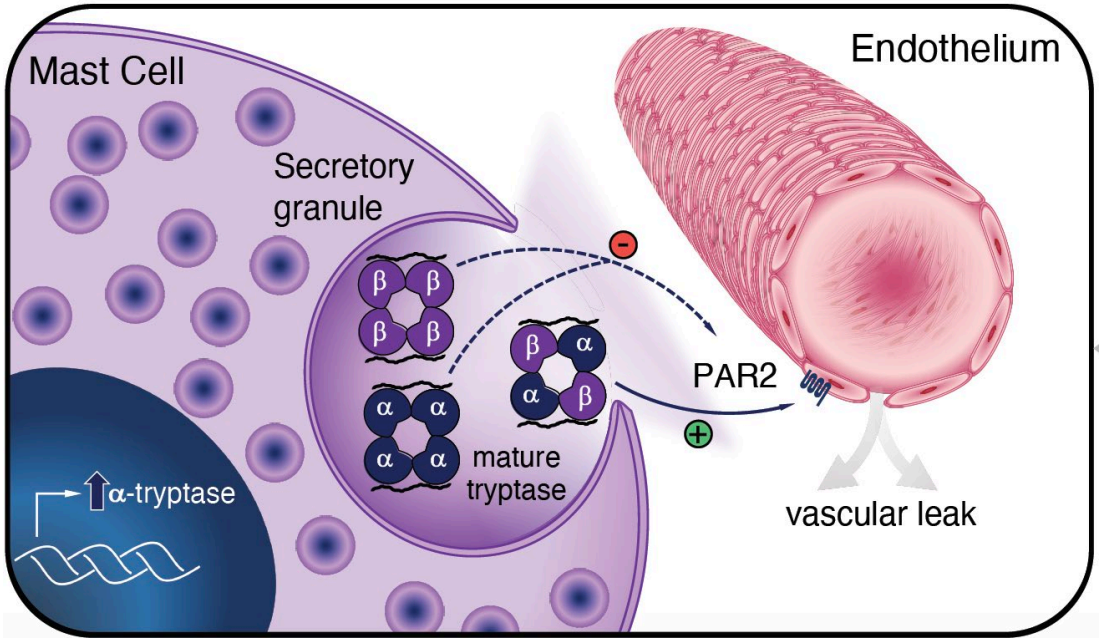






Le, Lyons et al. *J Exp Med.* 2019

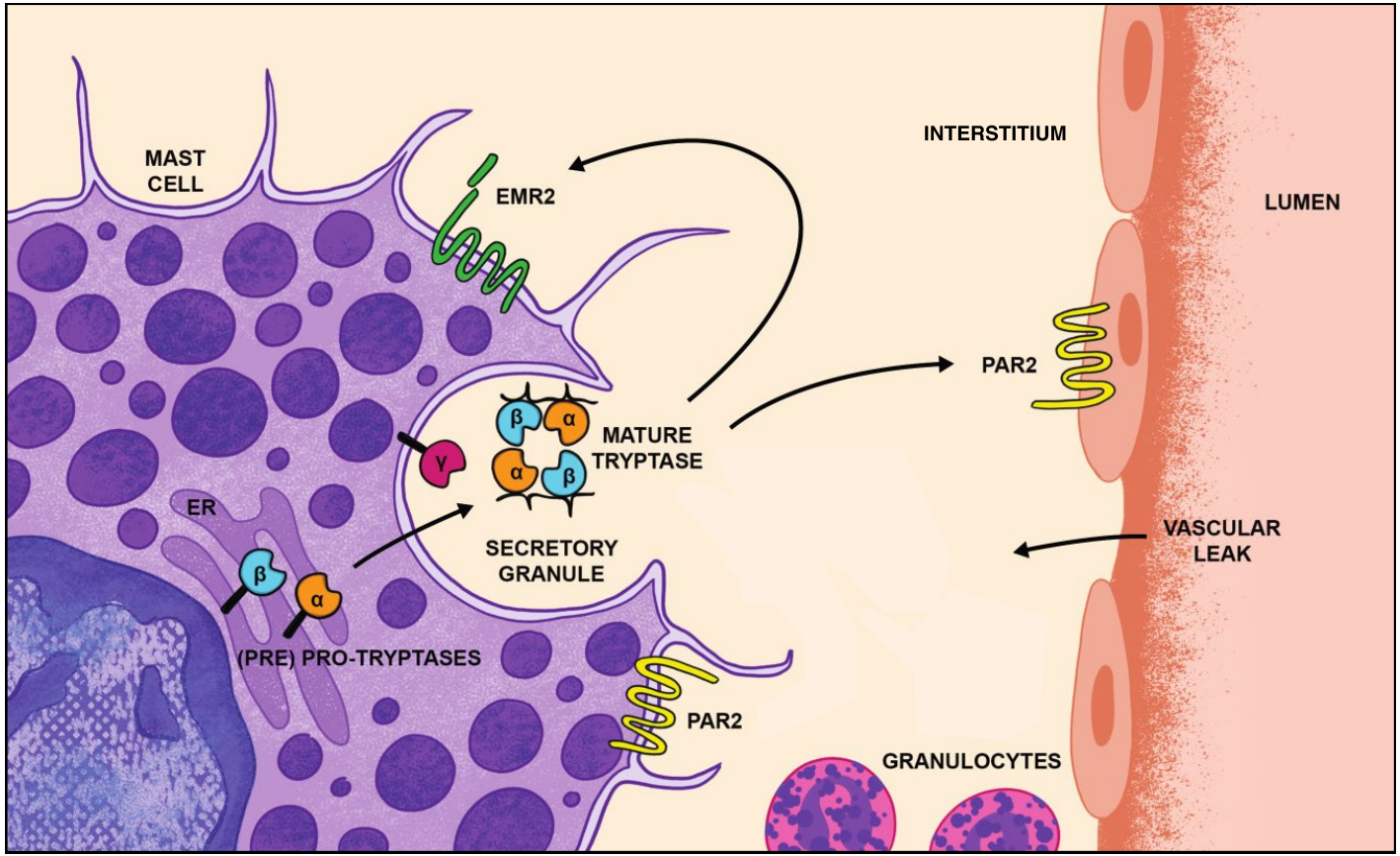
# α/β-Heterotetrameric tryptases selectively activate PAR2 to promote endothelial cell leak



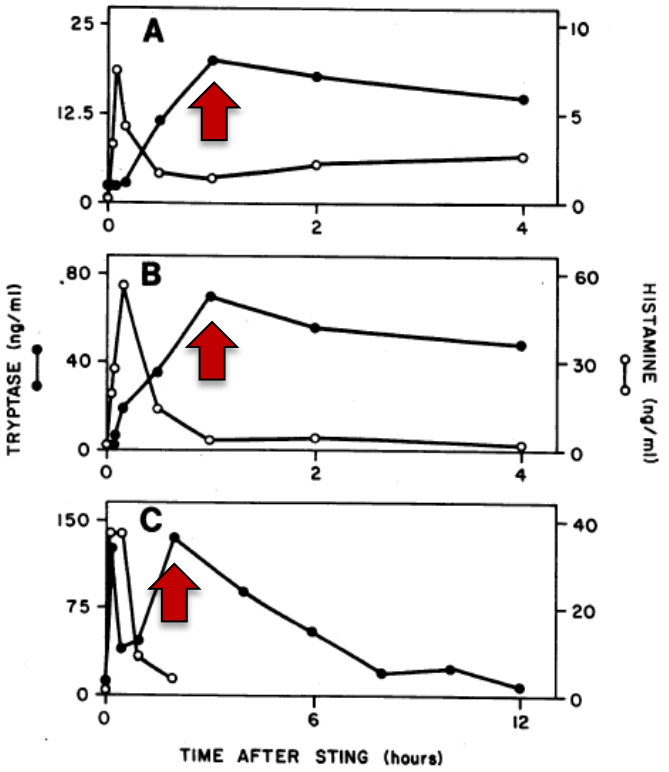

Lyons et al. *JACI.* 2021

# Autocrine and paracrine effects of α/β-tryptase heterotetramers that may augment immediate hypersensitivity



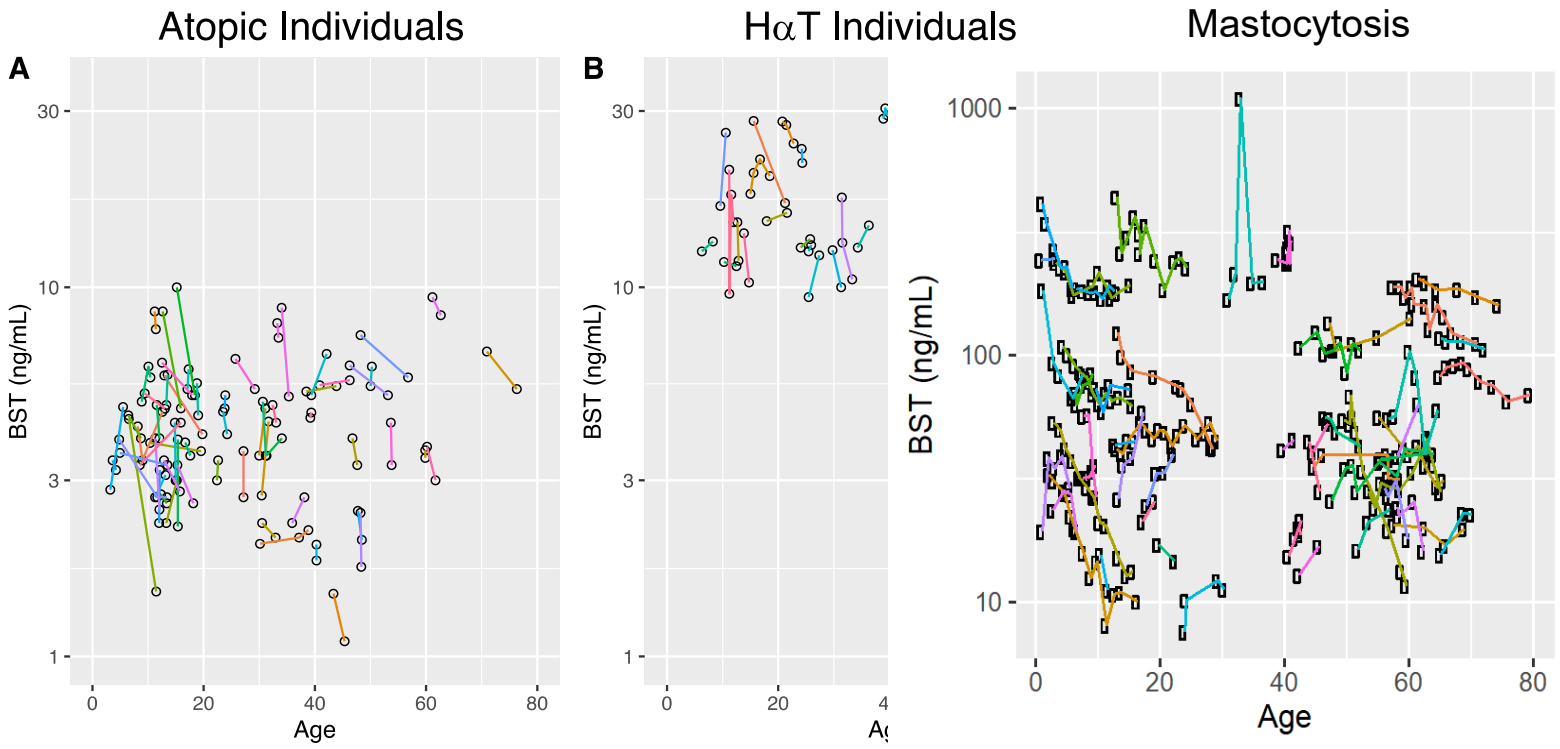

Wu and Lyons. *Curr Allergy Asthma Rep*. 2021

# An increase in total serum tryptase of 20% + 2 ng/mL over BST is the currently accepted standard for anaphylaxis



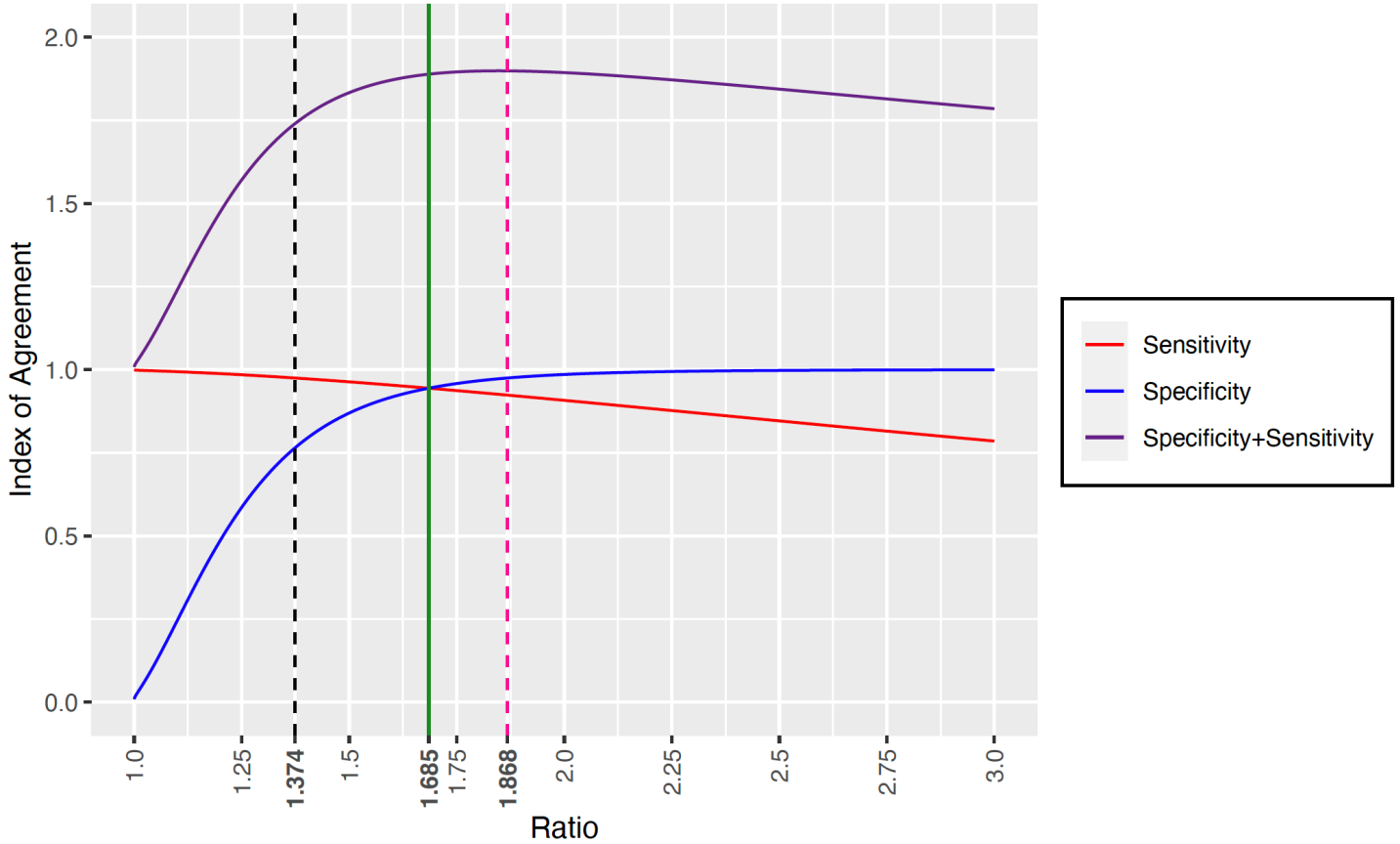

Schwartz et al. *J Clin Invest.* 1989

# BST levels exhibit substantial variability that negatively impacts the specificity 20%+2

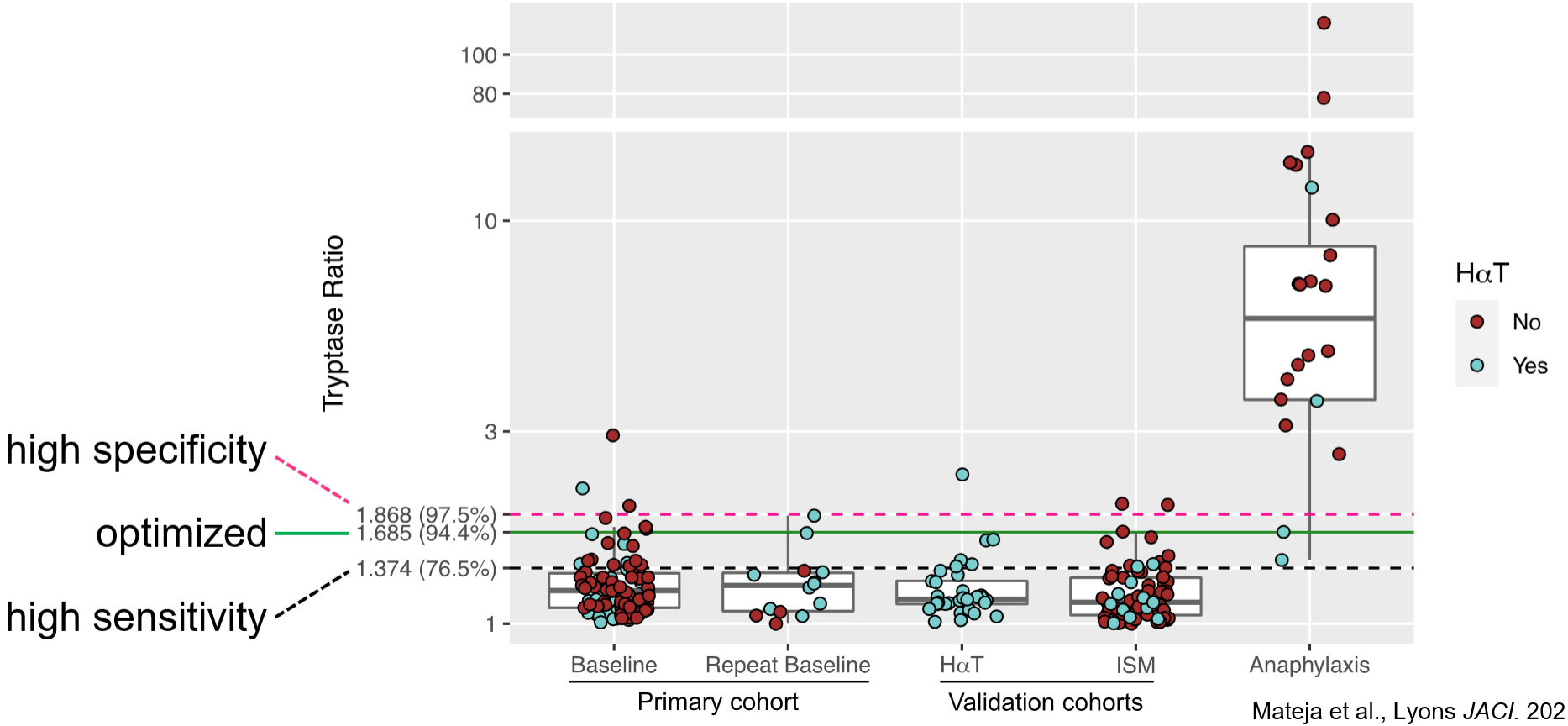



Mateja et al., Lyons *JACI.* 2021

# Modeling the data identifies simple ratios that maximize sensitivity, specificity, or their sum

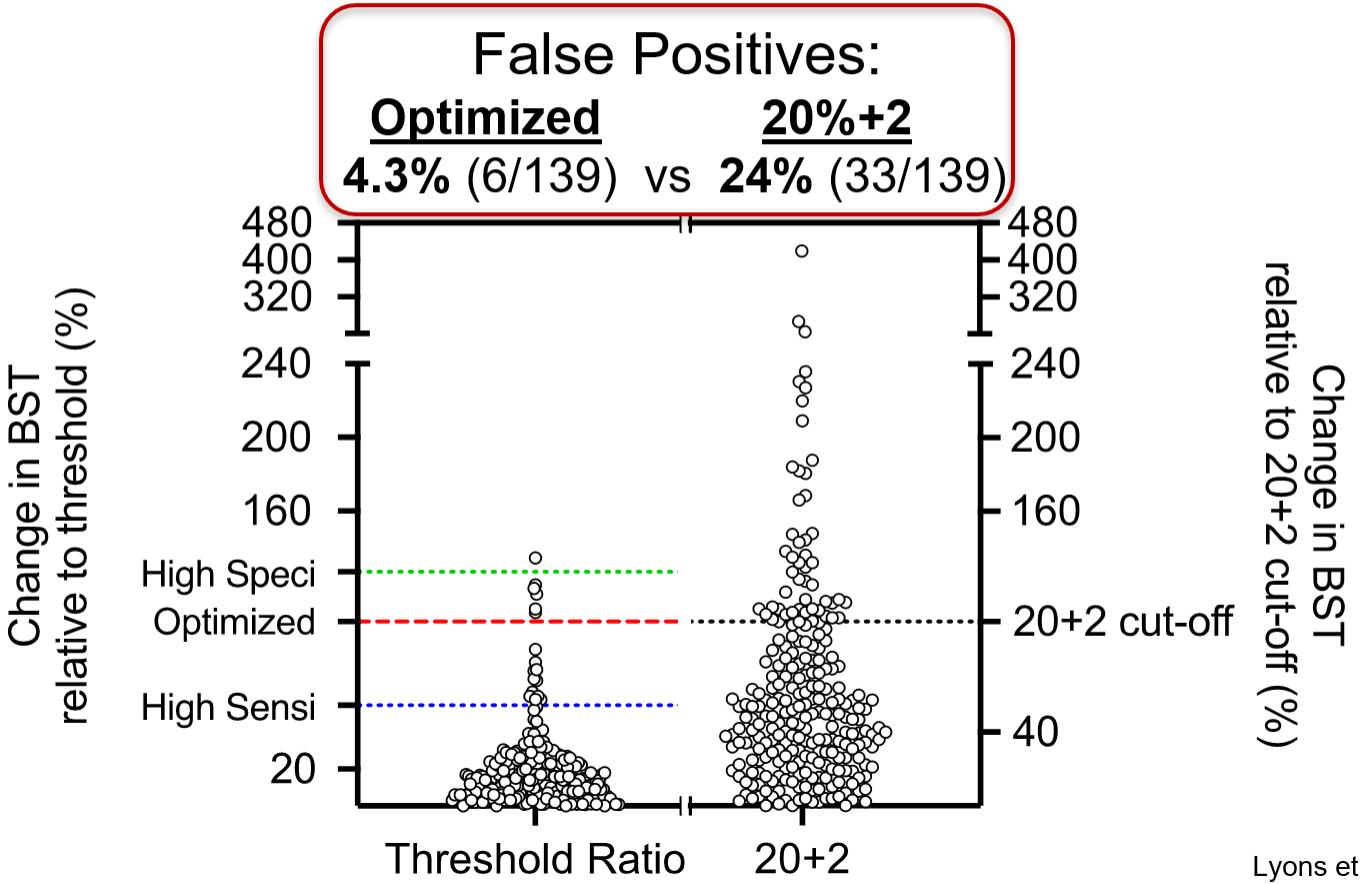


# Pre-test probability-based threshold ratios can maximize sensitivity or specificity based upon clinical scenario




Mateja et al., Lyons *JACI.* 2021

# A simple ratio of acute tryptase/BST improves specificity compared to 20%+2 when BST is elevated




Lyons et al. *JACI Pract.* 2022

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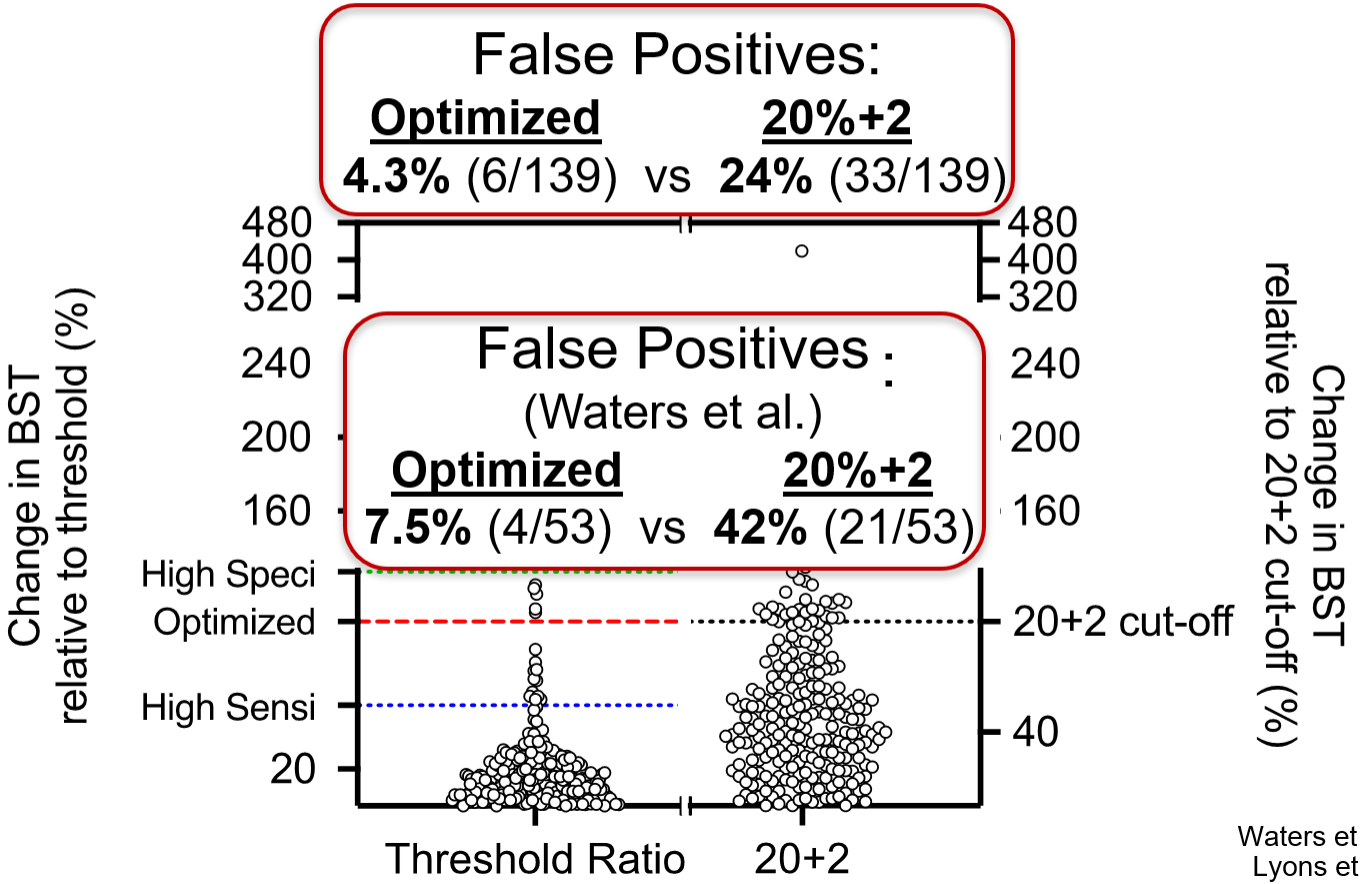



Waters et al. *JACI Pract.* 2022
Lyons et al. *JACI Pract.* 2022

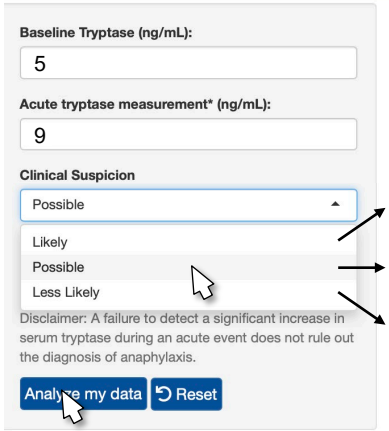

**https://triptase-calculator.niaid.nih.gov/**

Mateja et al., Lyons *JACI.* 2021

National Institute of Allergy and Infectious Diseases

*Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases*

# Total Rise In Peripheral Tryptase After Systemic Event (TRIPTASE) Calculator




High sensitivity (1.374)

Optimized (1.685)

High specificity (1.868)

This tool was developed by Translational Allergic Immunopathology Unit in collaboration with Bioinformatics and Computational Biosciences Branch (BCBB). For any questions regarding this tool, please contact Dr. Jonathan Lyons or Qinlu Wang.

Our manuscript describing the design and development of this tool can be found here (Link TBD).

National Institute of Allergy and Infectious Diseases

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# Total Rise In Peripheral Tryptase After Systemic Event (TRIPTASE) Calculator

**Baseline Tryptase (ng/mL):**

22

**Acute tryptase measurement* (ng/mL):**

30

**Clinical Suspicion**

Possible

*Total serum tryptase measured within 4 hours of symptom onset during an episode suggestive of a systemic immediate hypersensitivity reaction.

Disclaimer: A failure to detect a significant increase in serum tryptase during an acute event does not rule out the diagnosis of anaphylaxis.

Analyze my data | Reset

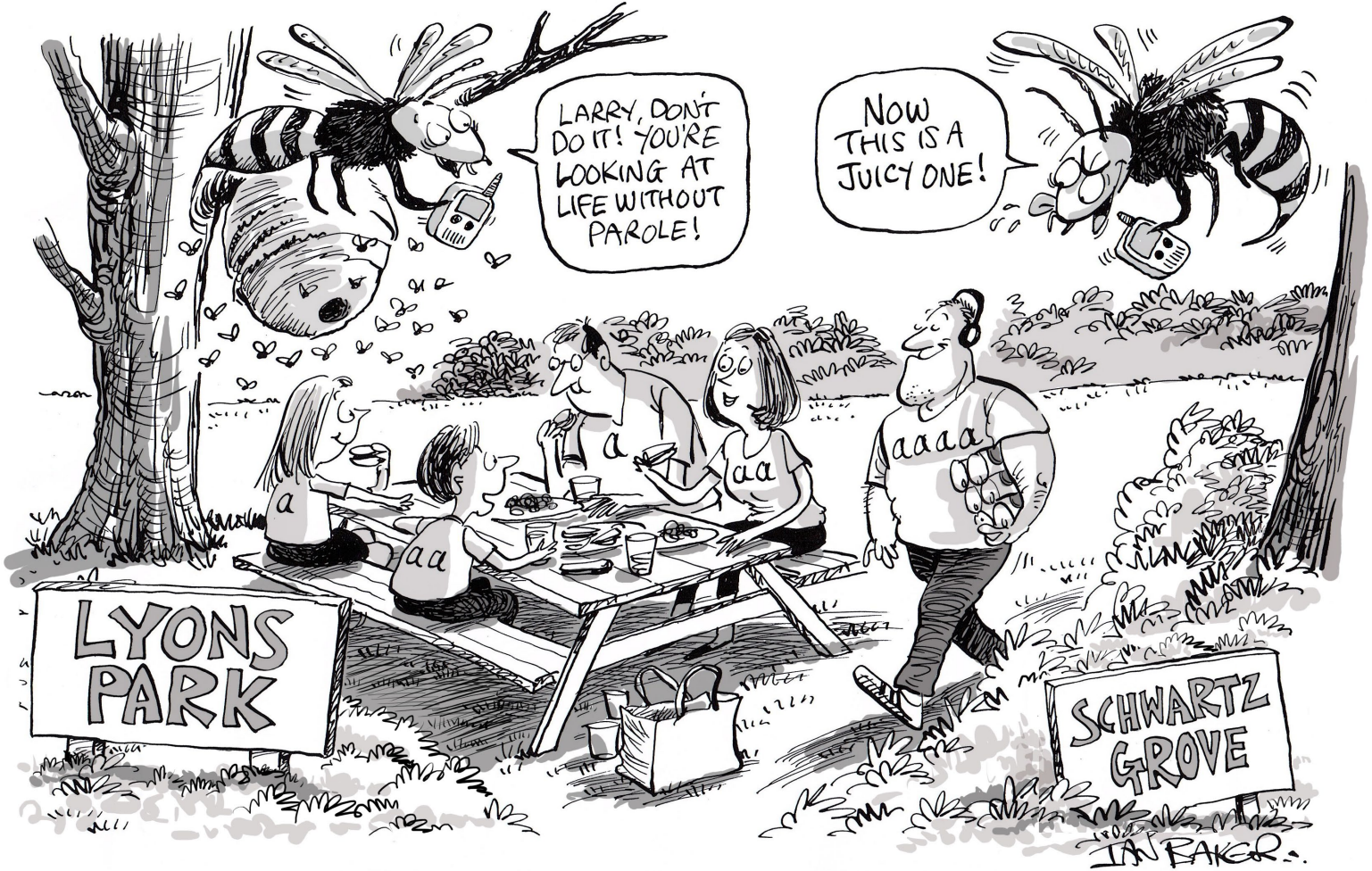
# Conclusions

- HαT is a common genetic trait caused by increased α-tryptase encoding *TPSAB1* copy number
- Elevated BST when encountered clinically is most often due to HαT
- BST >8 ng/mL is uncommon; >11.4 ng/mL when HαT is absent likely represents a clonal myeloid disorder
- HαT modifies symptom severity and anaphylaxis among individuals with clonal and non-clonal mast cell disorders
- Heterotetrameric tryptases have unique properties that may contribute to symptoms associated with HαT
- BST variability negatively impacts its use for diagnosis of mast cell activation using the current 20+2 method

# Resources

https://bst-calculater.niaid.nih.gov – for determining BST ranges based on genotype
*from Chovanec et al. *Blood Adv*. 2022

https://triptase-calculator.niaid.nih.gov/ – data-based refinement of 20% + 2 ng/mL
*from Mateja et al. *JACI*. 2021




PREMEDITATED MURDER HORNETS

Courtesy of Jason Gotlib