# Mast cell disorders, HaT, POTS and EDS: Sorting fact from fiction

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UC San Diego
SCHOOL OF MEDICINE

# Learning Objectives

- Describe the genetic basis for hereditary alpha-tryptasemia
- Identify clinical complaints associated with HαT
- Recognize the association between alpha-tryptase over-expression and mast cell-mediated symptoms
- Understand the proposed mechanistic basis for these associations

# Defining MCAS

**TABLE I.** Diagnostic consensus criteria for MCAS*

A. Typical clinical signs of severe, recurrent (episodic) systemic MCA are present (often in the form of anaphylaxis) (definition of systemic: involving at least 2 organ systems)

B. Involvement of MCs is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual's baseline to 120% + 2 ng/mL†

C. Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production, or drugs blocking mediator release or the effects of MC-derived mediators‡

Dog–allergic asthmatic who develops hives and wheezing after petting their friend's dog at a sleepover

Valent et al. *JACI Pract.* 2022

# Defining MCAS

**TABLE II.** Recognized variants of MCASs and estimated risk for development of life-threatening anaphylactic MCAS events

| Variant of MCAS | Main diagnostic features | Estimated risk for repeated severe anaphylaxis |
|---|---|---|
| Monoclonal MCAS<br>= clonal MCAS*<br>= primary MCAS* | The *KIT* D816V mutation is detected and MCs may display CD25 and/or CD30<br>(a) with confirmed ma<br>(b) only 2 minor SM criteria are met† | ++ |
| Secondary MCAS | An IgE-mediated allergy, another hypersensitivity reaction, or another immunolog diagnosed, but no neoplastic MCs or *KIT* D816V is found‡ | ++ |
| Combined MCAS | Criteria f HαT may also be dete | +++ |
| HαT$^{+}$ MCAS | HαT is de | +/++ |
| Idiopathic MCAS | Criteria to diagnose MCAS are met, but no related reactive disease, no IgE-dependent allergy, and no neoplastic/clonal MCs are detected; in addition,‖ no HαT is known or found | + |

Mastocytosis

Food allergy, venom allergy

Mastocytosis with venom allergy

HαT with food or venom allergy

Valent et al. *JACI Pract.* 2022

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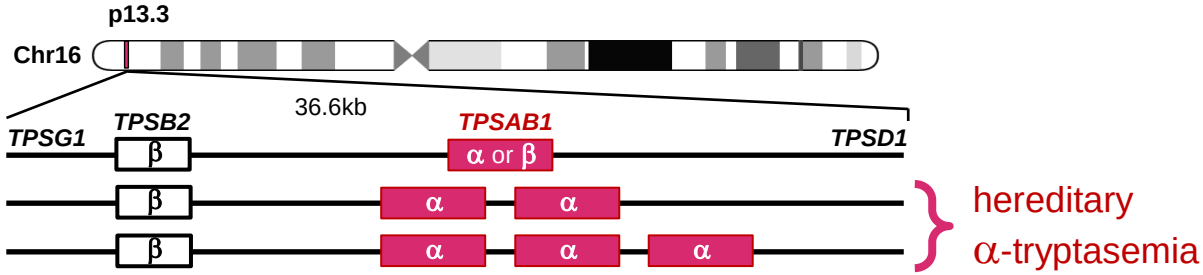
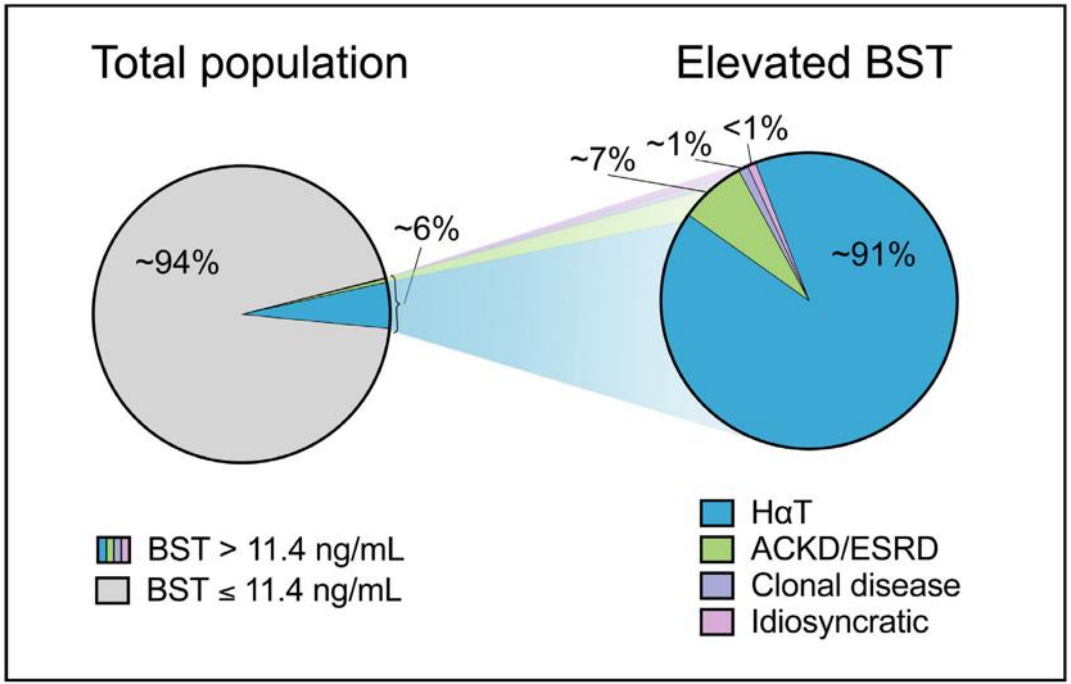
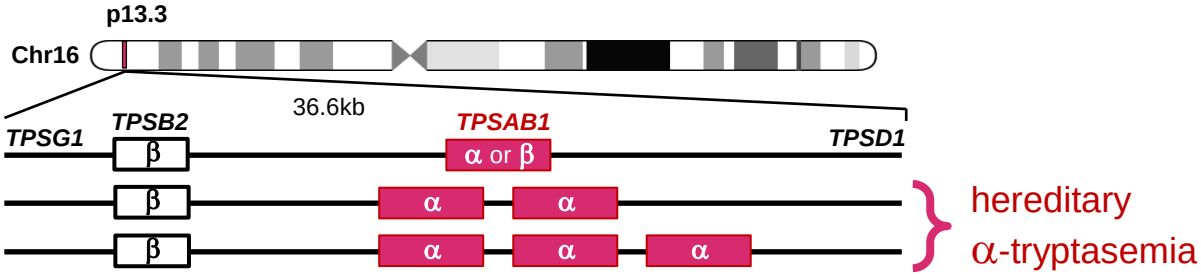
Valent et al. *JACI Pract.* 2022

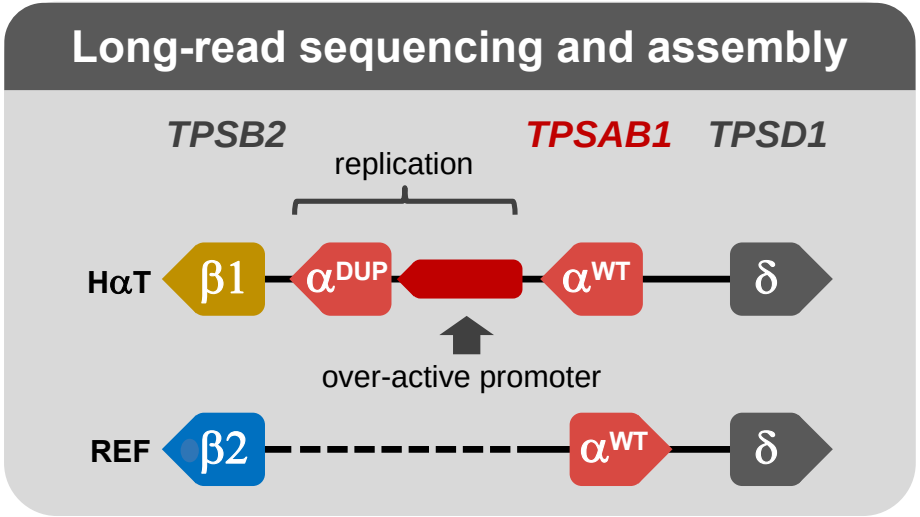



Lyons. *Ann Allergy Asthma Immunol.* 2021

Lyons et al. *Nat Genet.* 2016

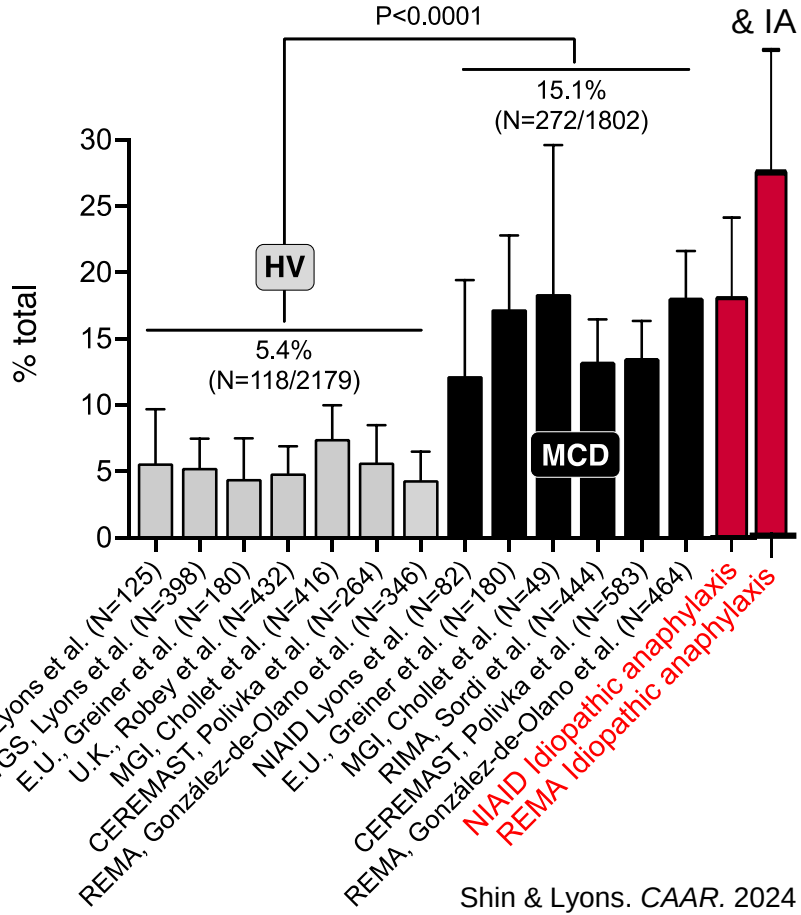


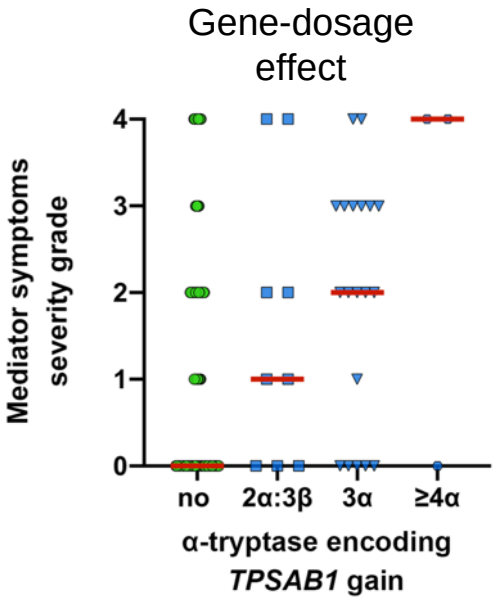

Chovanec et al., Lyons. *Blood Adv*. 2022

Lyons et al. *Nat Genet.* 2016

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

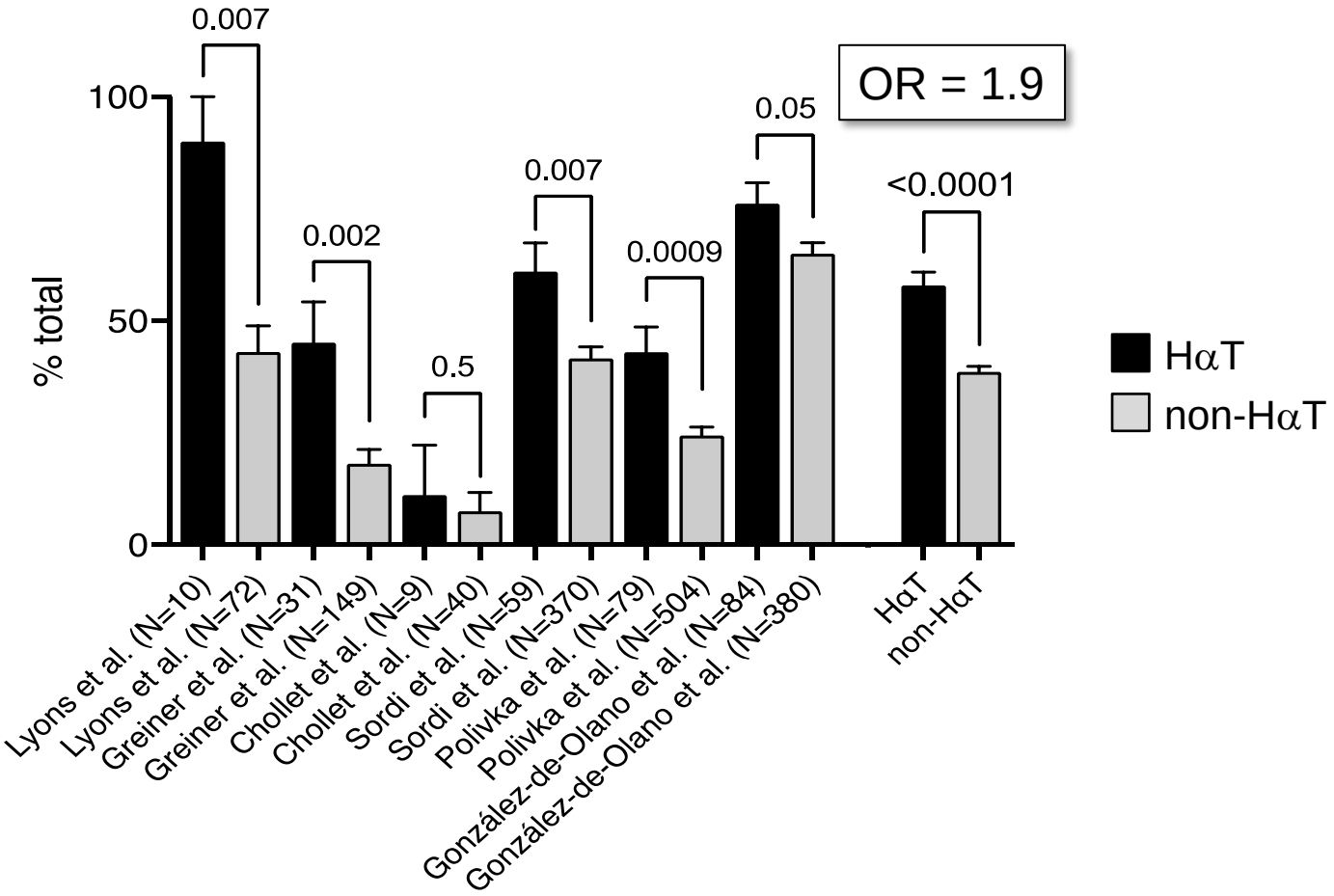



Shin & Lyons. *CAAR.* 2024

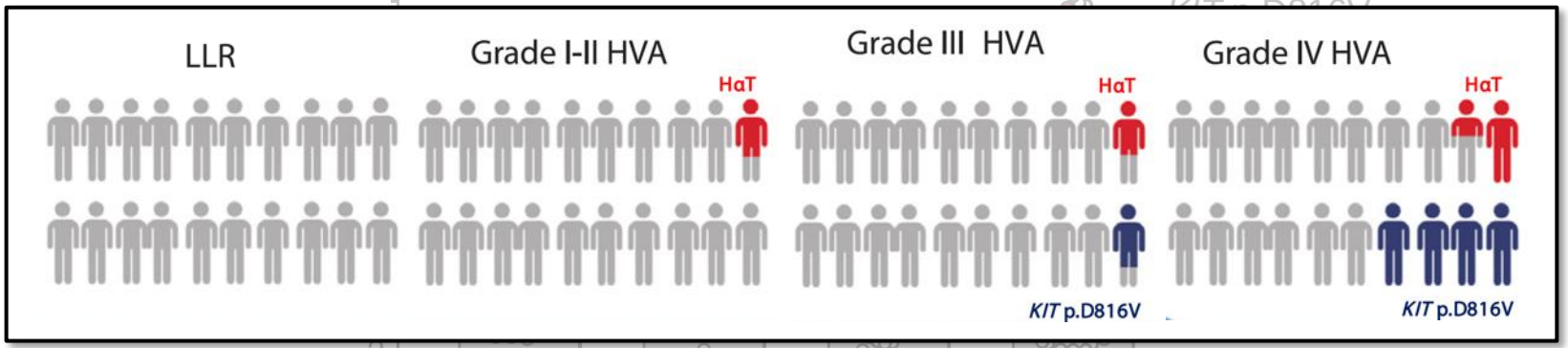



Greiner et al. *Blood.* 2020

# HαT is associated with anaphylaxis risk in MCD patients



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







N=881, OR=2.2, P=0.006

HαT

Systemic Mastocytosis (SM)

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

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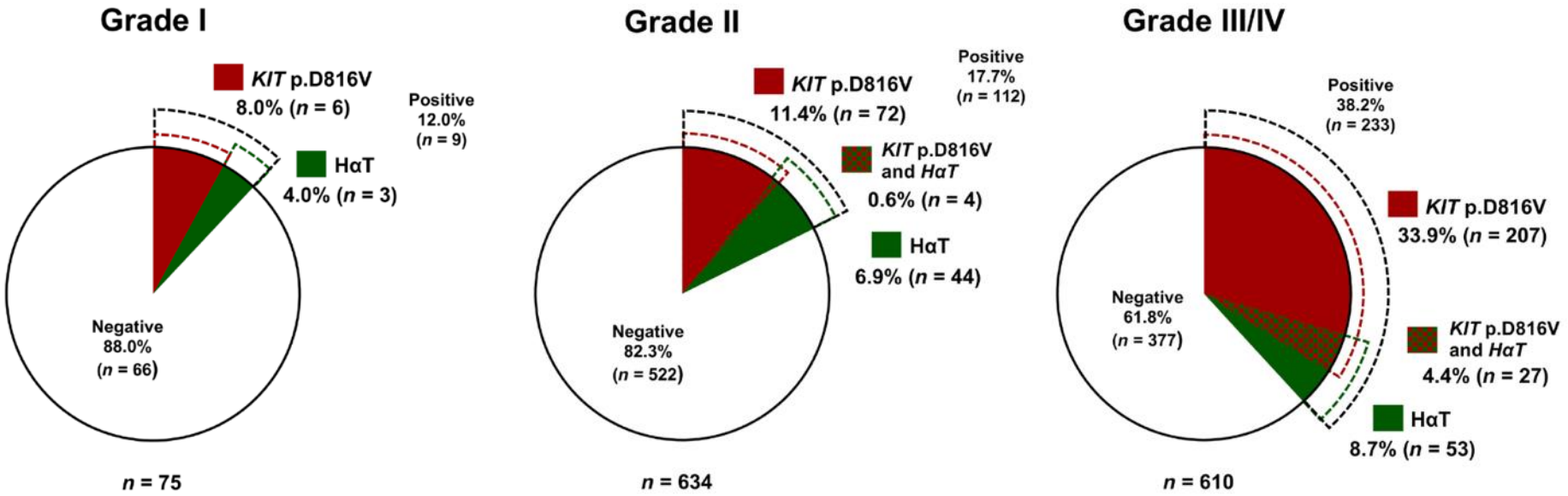
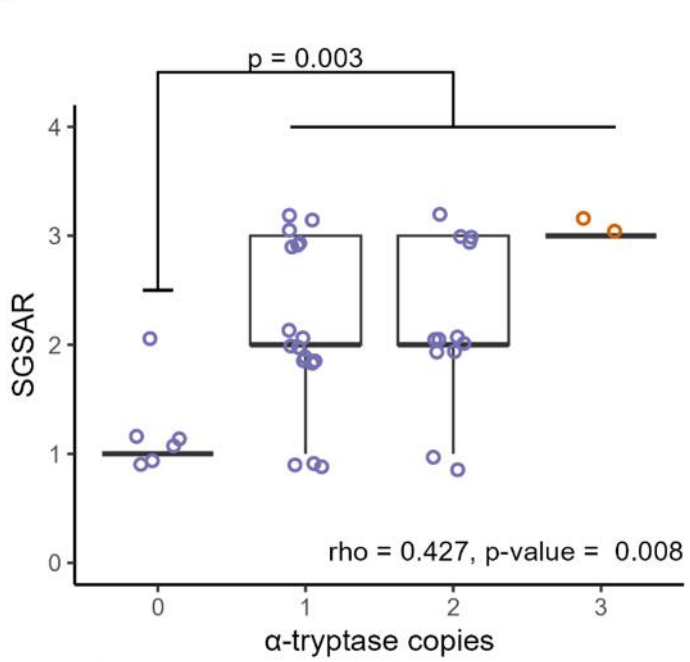
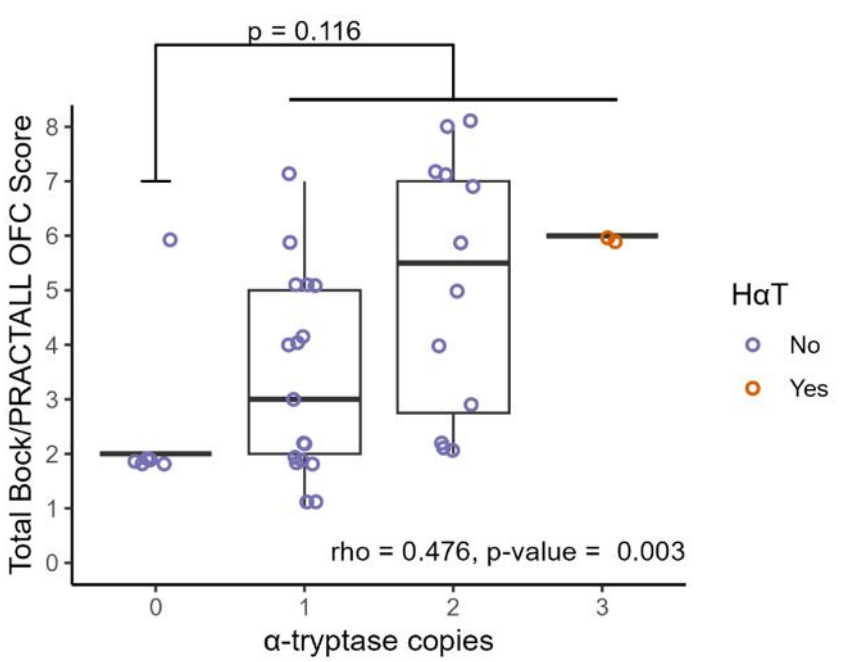



87% (27/31) with HαT and *KIT* p.D816V had Grade III/IV anaphylaxis

Korošec et al. *Allergy.* 2024

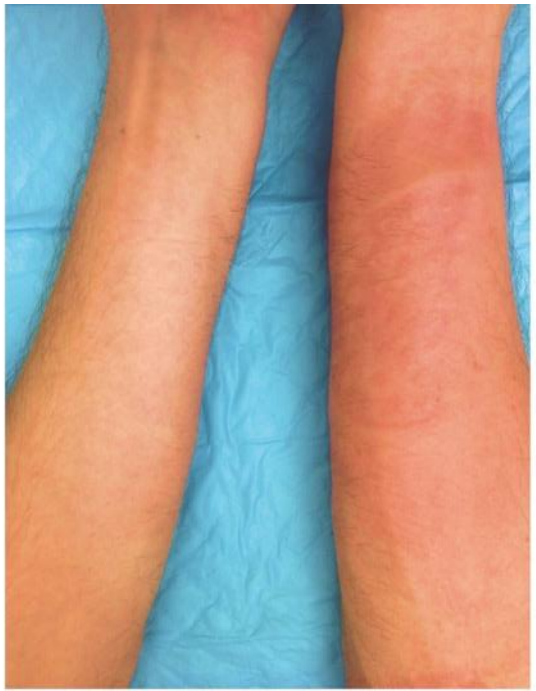
# Increased relative α-tryptase copy number: risk factor for food anaphylaxis severity

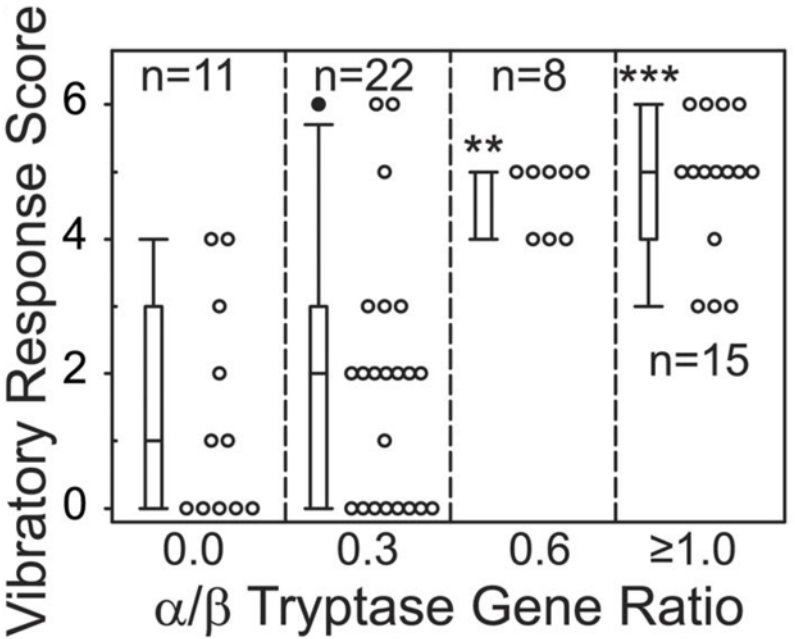



Lang et al., Lyons. *JACI.* 2023

# Increased relative α-tryptase copy number: linked to more severe reactions to vibratory challenge

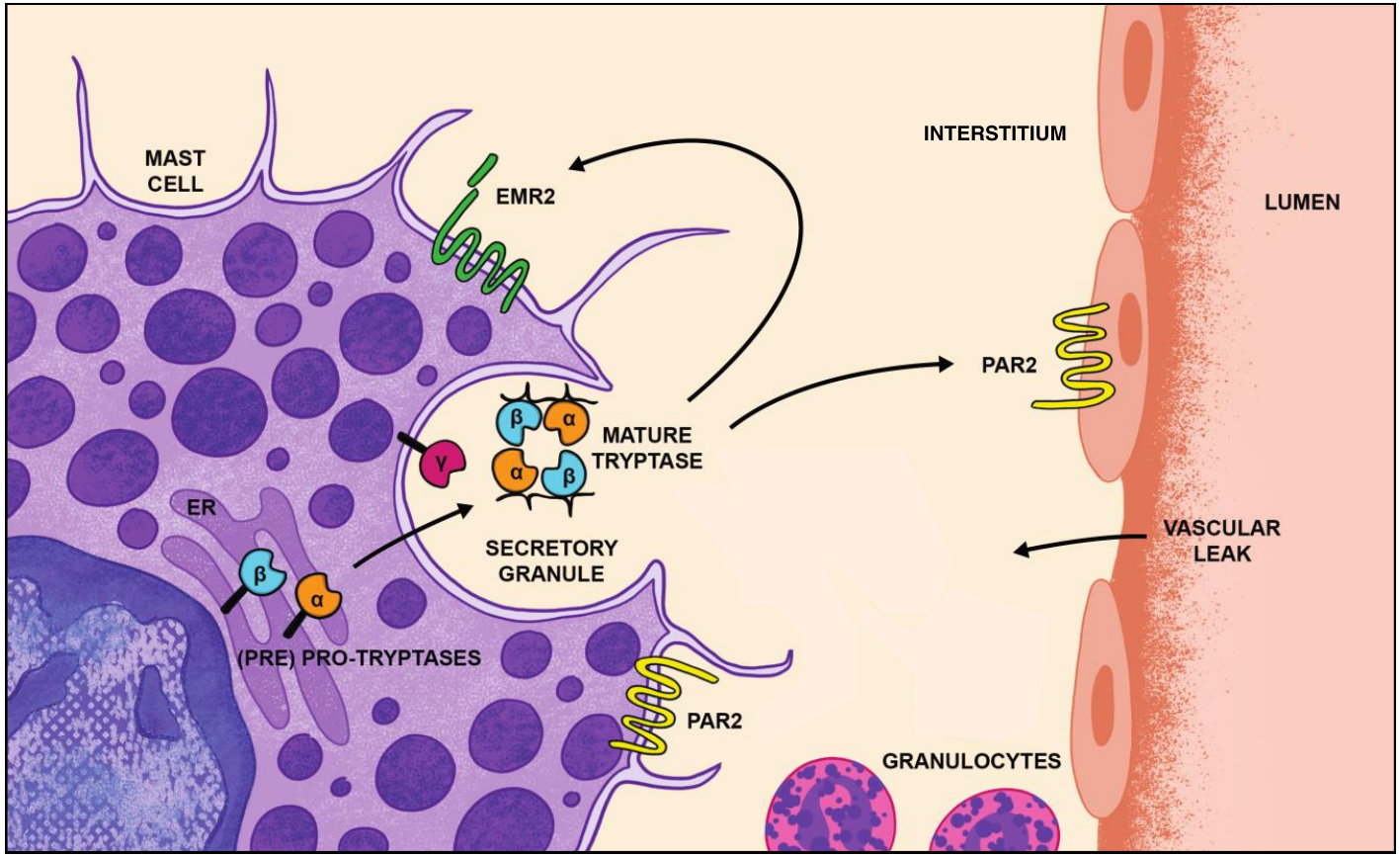





Lyons et al. *JACI* 2014

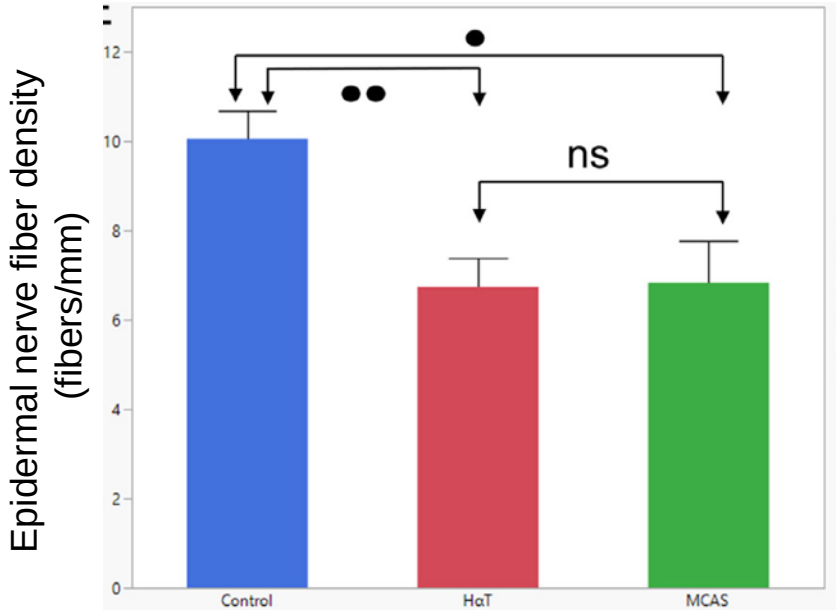
Le, Lyons et al. *J Exp Med.* 2019

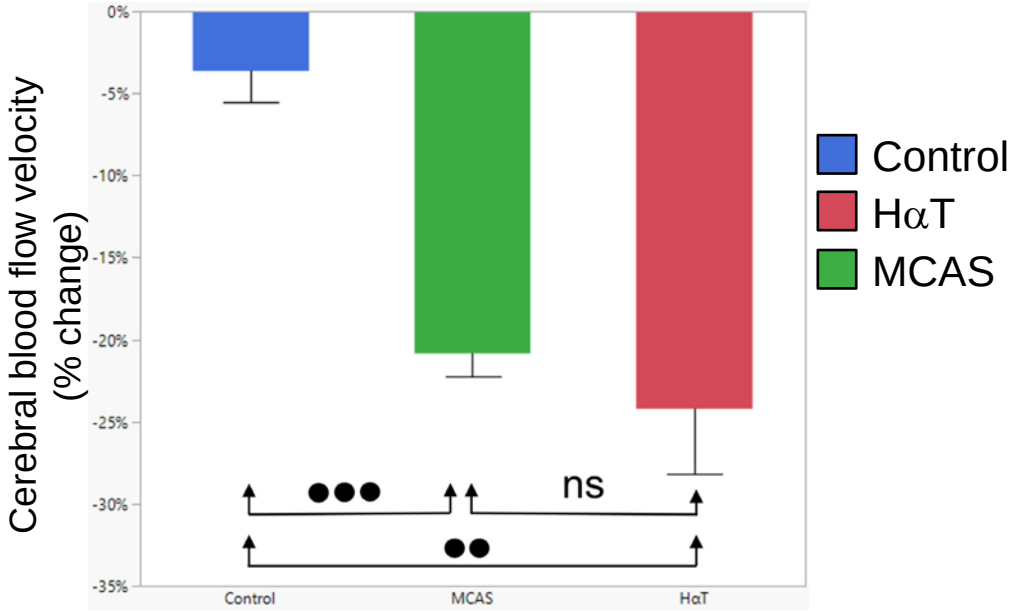
# α/β-Tryptase heterotetramers augment immediate mast cell-mediated reactions




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

# Decreased nerve density and cerebral blood flow in symptomatic individuals with HαT and MCAS




**Missing comparator of symptomatic individuals without these diagnoses*

*OCHOS, orthostatic cerebral hypoperfusion syndrome*

Novak et al. *Ann Allergy Asthma Immunol.* 2022

# HαT is not associated with POTS

**TABLE II.** bST levels

| Serum tryptase value (ng/mL) | No. of patients | No. of patients with genetic testing for HαT | No. of patients with positive genetic testing result for HαT |
|---|---|---|---|
| <2 ng/mL | 16 | 0 | 0 |
| 2-6.4 ng/mL | 207 | 0 | 0 |
| 6.5-8 ng/mL | 9 | 4 | 0 |
| 8-11.4 ng/mL | 9 | 1 | 1 |
| >11.4 ng/mL | 9 | 4 | 4 |

bST levels were available for 250 patients diagnosed with POTS via tilt-table testing. Most (232) were <8 ng/mL. A total of 18 patients had levels >8 ng/mL, corresponding with increased likelihood of HαT.

Only 18/250 (7.2%) of POTS patients had BST > 8ng/mL

Huang et al. *JACI Pract.* 2024

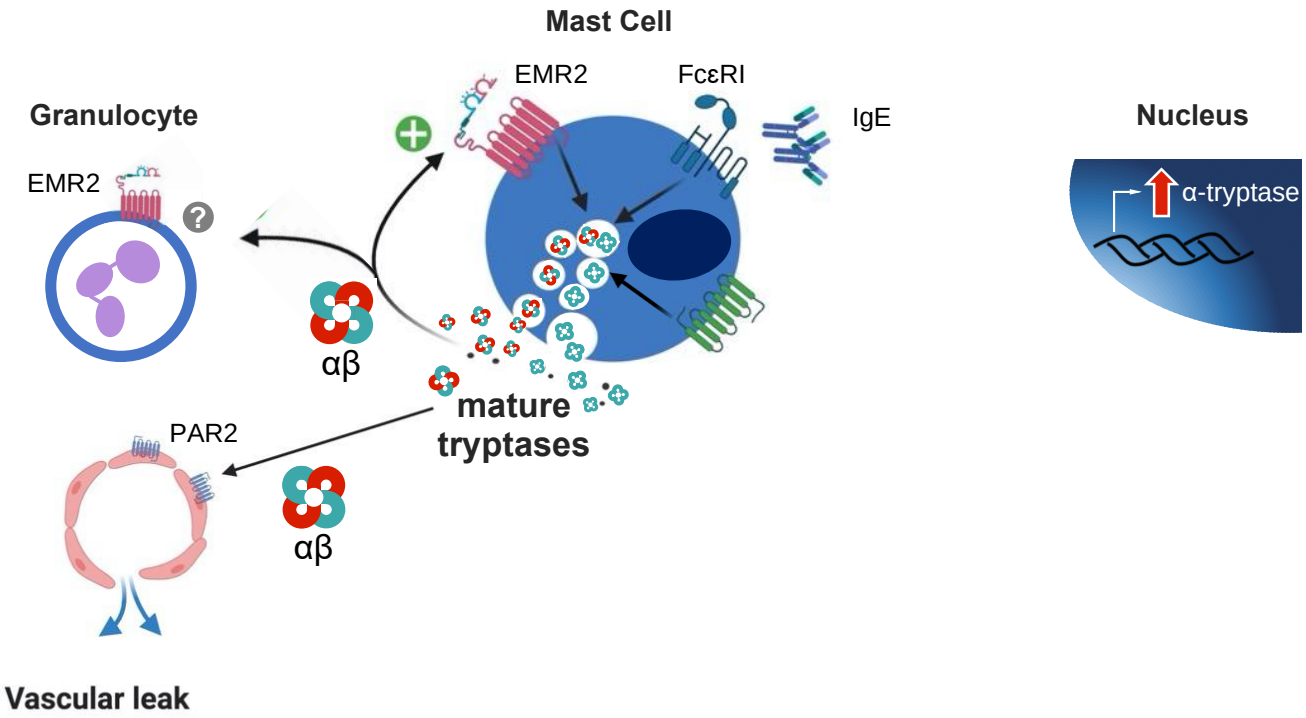
# HαT is not associated with congenital hypermobility – but may modify symptoms

| | HSD, hEDS, and axial skeletal abnormality with hypermobility | | | | |
|---|---|---|---|---|---|
| | HαT (n = 11) | no HαT (n = 225) | | | |
| **Manifestation** | **n (%)** | **n (%)** | **OR** | **RR** | **p value** |
| Anaphylaxis | 2 (18) | 8 (4) | 5.9 (1.1–26.4) | 5.0 (1.3–17.1) | 0.07 |
| Pruritus | 5 (56) | 51 (39) | 1.9 (0.5–6.5) | 1.4 (0.7–2.3) | 0.5 |
| Inflammatory bowel disease | 0 (0) | 3 (1) | 0 (0.0–24.1) | 0 (0.0–22.2) | >0.99 |
| Retained primary dentition* | 3 (27) | 1 (0) | 81 (10.2–1,048) | 59.2 (8.7–387.8) | 0.0003 |
| Headache and/or migraine | 8 (73) | 146 (70) | 1.1 (0.3–4.1) | 1.1 (0.6–1.3) | 0.7 |
| Sleep disturbances | 9 (90) | 116 (78) | 2.5 (0.4–28.0) | 1.1 (0.8–1.3) | 0.06 |
| Dysphagia* | 8 (73) | 61 (31) | 5.9 (1.7–21.1) | 2.3 (1.4–3.3) | 0.007 |
| Chronic fatigue | 10 (91) | 193 (88) | 1.4 (0.2–15.7) | 1.0 (0.7–1.2) | >0.99 |
| Neurological bladder | 0 (0) | 5 (2) | 0 (0.7–1.0) | 0 (0.0–14.7) | >0.99 |

4.8% with HαT

4.2% with anaphylaxis

Vazquez et al, Lyons. *HGG Adv.* 2022




Glover et al., Lyons. *Annals*. 2021

# Conclusions

- HαT is a natural over-expression model of alpha-tryptase
- Increased relative abundance of alpha-tryptase is associated with more severe MC-mediated reactions
- Symptomatic individuals with MCAS and HαT have abnormal nerve density and cerebral perfusion during tilt-table testing
- HαT is not associated with POTS or congenital hypermobility
- Among POTS patients, HαT is associated with dysphagia, retained teeth, and non-significant increases in anaphylaxis and pruritus
- HαT is common so caution must be used such that misattribution of symptoms does not occur
- More studies are needed to better characterize how HαT may impact these and other phenotypes where tryptases are implicated