Analysis of Hereditary Alpha Tryptasemia and Association With Baseline Characteristics in Patients With Indolent Systemic Mastocytosis Enrolled on the PIONEER Study

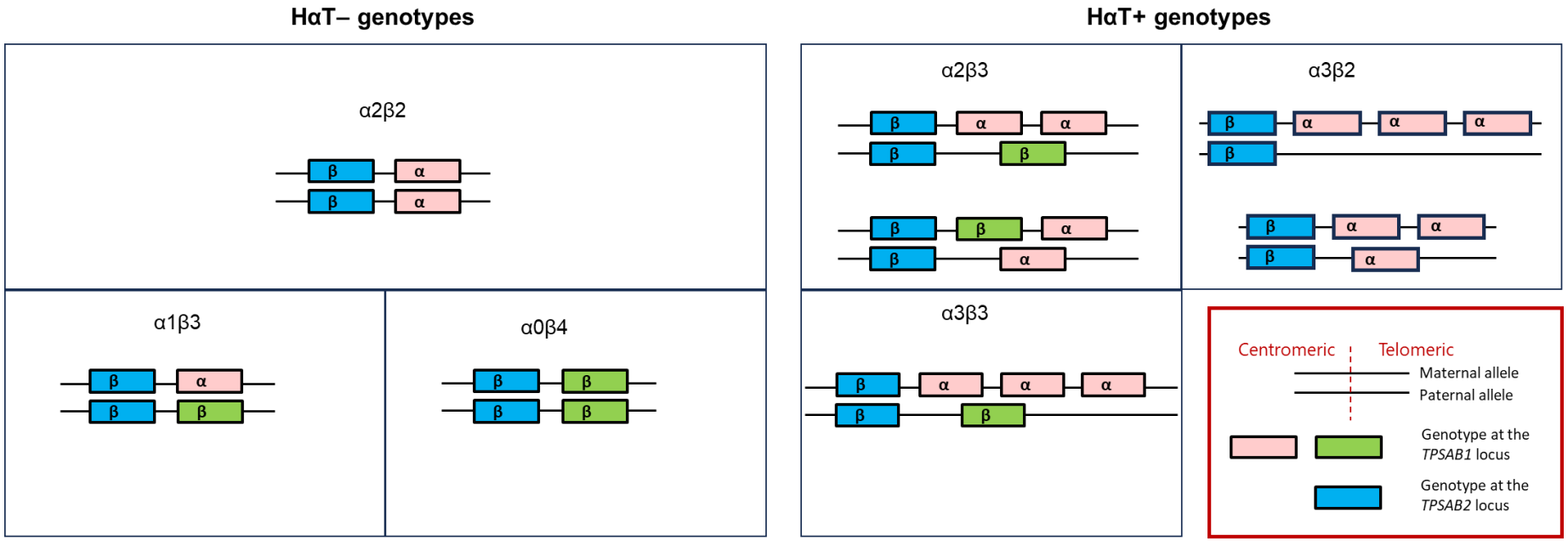
Mariana Castells,[1] Cem Akin,[2] Marcus Maurer,[3,4] Karin Hartmann,[5,6] Sigurd Broesby-Olsen,[7] Tracy I. George,[8] Frank Siebenhaar,[3,4] Kate Newberry,[9] Guang Yang,[9] Ben Lampson,[9] Alberto Orfao[10]

[1]Department of Medicine, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]University of Michigan, Ann Arbor, MI, USA; [3]Institute of Allergology, Charité–Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [4]Fraunhofer Institute for Translational Medicine and Pharmacology, Allergology and Immunology, Berlin, Germany; [5]Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland; [6]Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland; [7]Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark; [8]ARUP Laboratories, Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT, USA; [9]Blueprint Medicines Corporation, Cambridge, MA, USA; [10]Centro de Investigación del Cáncer, Universidad de Salamanca-CSIC, Salamanca, Spain

American Initiative in Mast Cell Diseases (AIM) Conference, Boston, MA; May 18–19, 2024

Hereditary α-tryptasemia (HαT)

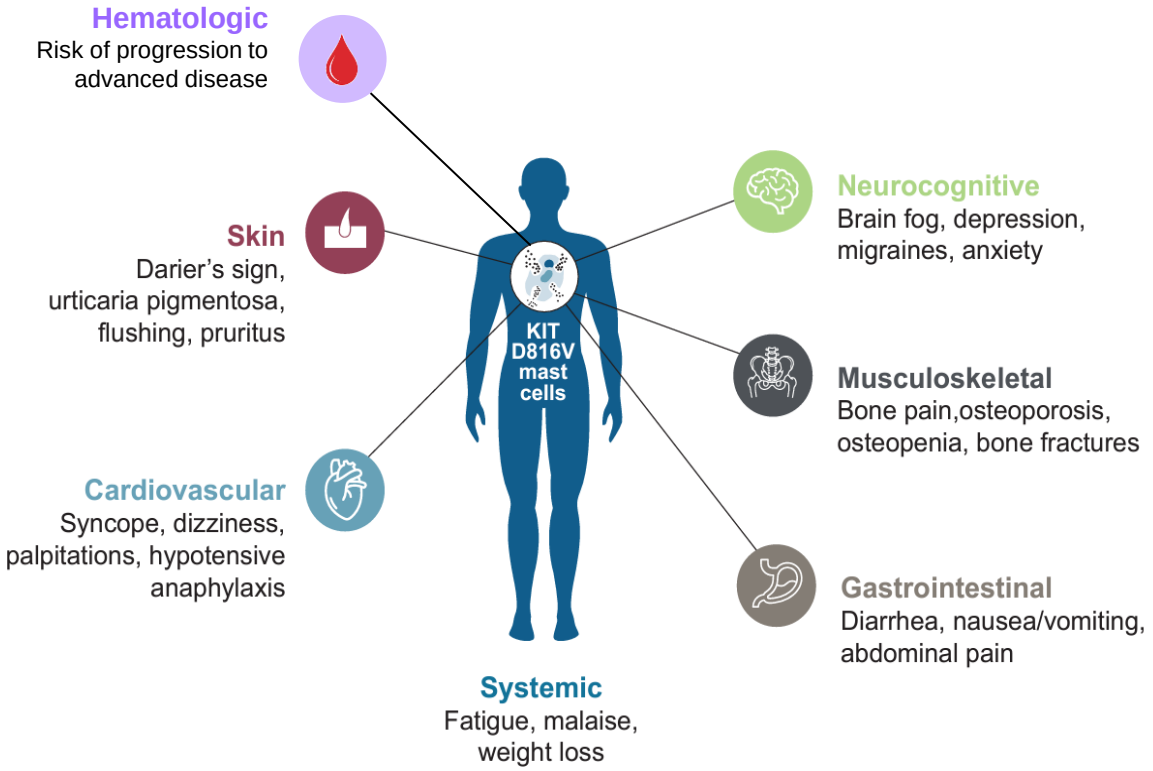
- HαT is a genetic trait defined by an increased *TPSAB1* gene copy number coding for alpha tryptase. This leads to elevated serum levels of tryptase, a protein produced by mast cells (MCs)[1–4]
  - *TPSAB1* encodes for the α allele (which may be present in multiple copies) or the β allele
  - *TPSAB2* encodes for the β allele only[2]
- HαT can be associated with symptoms of MC diseases such as anaphylaxis, gastrointestinal symptoms, and skin symptoms[1–4]



1. Wu R et al. *Curr Allergy Asthma Rep*. 2021;21; 2. Chollet MB et al. *J Allergy Clin Immunol.* 2022;149:728–735; 3. González-de-Olano D et al. *Allergy*. 2024;79:711–723; 4. Giannetti MP et al. *Ann Allergy Asthma Immunol.* 2021;126:655–660

Patients with SM have higher rates of HαT than the general population

- HαT is present in 4–6% of the general population[1–3]
- Systemic mastocytosis (SM) is a clonal mast cell disease, driven by the *KIT* D816V mutation
  - Patients with SM may experience life-long debilitating symptoms and disease progression[4–6]
  - Elevated tryptase is one of the minor diagnostic criteria although not all patients with SM experience high serum tryptase levels[4–6]
- Presence of HαT may overlap with SM and having both is associated with increased risk of severe anaphylaxis[1–3]



Recent studies have found that HαT is present in 9–18% of patients with SM[1–3]

1. Lyons JJ et al. *J Allergy Clin Immunol*. 2021;147(2):622–632; 2. González-de-Olano D et al. *Allergy*. 2024;79:711–723; 3. Chollet MB et al. *J Allergy Clin Immunol.* 2022;149:728–735; 4. Pardanani A. *Am J Hematol*. 2023;98:1097–1116; 5. Ungerstedt J et al. *Cancers*. 2022;14:3942; 6. Mukherjee S et al. Presented at ASH 2022. Poster #3053

PIONEER allowed the evaluation of the relationship between HαT and SM

- PIONEER (NCT03731260): Randomized, double-blind, placebo-controlled study in patients with indolent systemic mastocytosis (ISM)
  - Avapritinib is a potent and highly selective oral therapy targeting KIT D816V, the underlying driver of SM
  - The safety, efficacy, and quality of life in patients with ISM receiving avapritinib plus best supportive care (BSC) compared with patients receiving placebo plus BSC were evaluated
  - A total of 250 patients were screened for HαT (positive, HαT+; negative, HαT–) by digital polymerase chain reaction detection of copy number variations of the *TPSAB1* gene on the tryptase locus[a]
  - Baseline objective measures of disease burden were recorded; *KIT* D816V variant allele fraction (VAF), serum tryptase levels, bone marrow (BM) MCs, and skin MCs

The cohort of patients enrolled on the PIONEER study represent one of the largest, most well characterized populations of patients with ISM to date

Here, we use this rare opportunity to compare baseline objective disease and symptom burden in HαT+ *versus* HαT– patients with ISM

[a]Testing was carried out by Virant Diagnostics, Wheaton, MD.

Gotlib J et al. *NEJM Evid*. 2023;2:EVIDoa2200339

Patient baseline characteristics were similar between groups

In patients screened, 11% (28/250) were HαT+

- Of the HαT+ patients, 14 had the *α2β3* genotype, 12 had the *α3β2* genotype, and two had the *α3β3* genotype
- The median age of patients who were HαT+ was slightly younger than that of patients who were HαT– (P=0.01) and prior therapies were similar across groups

	Patients	
	HαT+ (N=28)	HαT– (N=222)
Age (years), median (range)	46 (21–64)	51 (18–79)
Female, n (%)	22 (79)	161 (73)
Corticosteroid use for SM, n (%)	3 (11)	17 (8)
Prior TKI therapy, n (%)	1 (4)	16 (7)
Prior cytoreductive therapy, n (%)	4 (14)	27 (12)

SM, systemic mastocytosis; TKI, tyrosine kinase inhibitor.

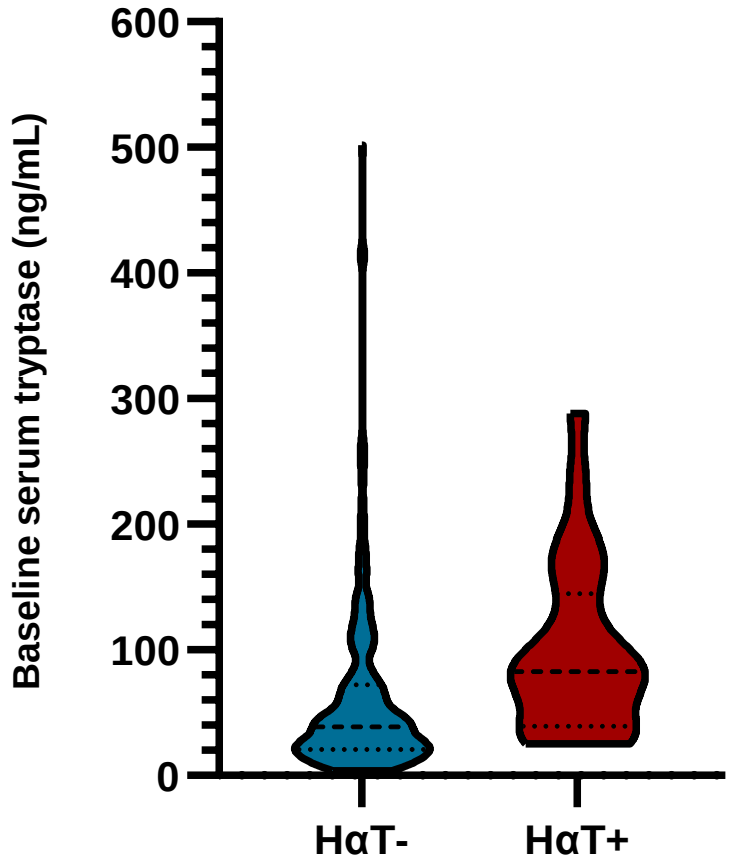
Baseline tryptase and *KIT* D816V VAF were significantly different between HαT+ and HαT– patients

- **Baseline serum tryptase was significantly higher in HαT+ patients**
- **Baseline *KIT* D816V VAF in the peripheral blood was significantly lower in HαT+ patients**
- BM MC burden was similar in patients with and without HαT
- No patients with HαT had palpable spleens or palpable livers
- Additionally, history of anaphylaxis was similar in patients with and without HαT

	Patients		P-value
	HαT+ (N=28)	HαT– (N=222)	
Median serum tryptase, ng/mL (range)	82.6 (25.2–288.0)	38.6 (3.6–501.6)	0.0001
Serum tryptase >20 ng/mL, n (%)	28 (100)	171 (77)	NA
Median *KIT* D816V VAF, % (range)	0.06 (0.0–16.2)	0.40 (0.0–41.3)	0.0004
Median BM MC burden, % (range)	6.0 (2.0–30.0)	7.0 (1.0–70.0)	ns
MC aggregates present, n (%)	20 (71)	177 (80)	NA
Median lesional skin MC density, counts/mm^2 (range)	336 (83–4300)	489 (53–2870)	ns
Median non-lesional skin MC density, counts/mm^2 (range)	114 (61–1337)	130 (10–659)	ns
Palpable spleens, n (%)	0 (0)	4 (2)	ns
Palpable livers, n (%)	0 (0)	12 (6)	ns
Anaphylaxis, n (%)	5 (18)	37 (17)	ns

VAF, variant allele freqeuency; BM, bone marrow; MC, mast cell; NA; not assessed; ns, not significant.

Baseline serum tryptase levels were higher in the HαT+ group



	Patients		P-value
	HαT+ (N=28)	HαT– (N=222)	
Serum tryptase levels, median ng/mL (range)	82.6 (25.2–288.0)	38.6 (3.6–501.6)	0.0001

- No HαT+ patients (n=28) with moderate-to-severe ISM had a baseline serum tryptase of <20 ng/mL
- Of the HαT– patients with moderate-to-severe ISM, 23% (n=222) had a baseline serum tryptase of <20 ng/mL

Regardless of HαT status, patients had similar response to avapritinib therapy[a]

	HαT+ patients	HαT– patients
Mean percent change in serum tryptase at 24 weeks	–51% (n=18)	–45% (n=116)
Mean percent change in *KIT* D816V VAF at 24 weeks	–54% (n=11)	–56% (n=98)
Mean percent change in ISM-SAF TSS at 24 weeks	–32% (n=17)	–33% (n=114)

[a]Data is restricted to Part 2 (randomized, double-blind, placebo-controlled) patients only.
ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form (©2018 Blueprint Medicines Corporation); TSS, total symptom score.

Conclusions

- The prevalence of HαT in the PIONEER population was 11%, which is consistent with previously reported frequencies of HαT in patients with ISM
- Compared to patients without HαT, patients with HαT had significantly higher baseline tryptase values and significantly lower *KIT* D816V VAF in the peripheral blood
  - There were no differences in the rate of anaphylaxis or ISM-SAF TSS at baseline
- Regardless of HαT status, patients had similar symptom and disease biomarker reductions after treatment with avapritinib

Acknowledgements

- We thank the patients and their families for making the PIONEER study possible
- We also thank the investigators and clinical trial teams who participated in the study
- Medical writing support was provided by Hannah Boyd, PhD, and Travis Taylor, BA, of Paragon (a division of Prime, Knutsford, UK). Funded by Blueprint Medicines Corporation. The sponsor reviewed and provided feedback on the presentation. However, the authors had full editorial control and provided final approval of all content