EDS ECHO SUMMIT SERIES

PRESENTATION

Disorders of Mast Cells and Mast Cell Activation

SPEAKER

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Brigham and Women's Hospital
Harvard School of Medicine


Brigham and Women's Hospital
Hale Building for Transformative Medicine

COVID-19 infection in patients with mast cell disorders including mastocytosis does not impact mast cell activation symptoms

Authors:

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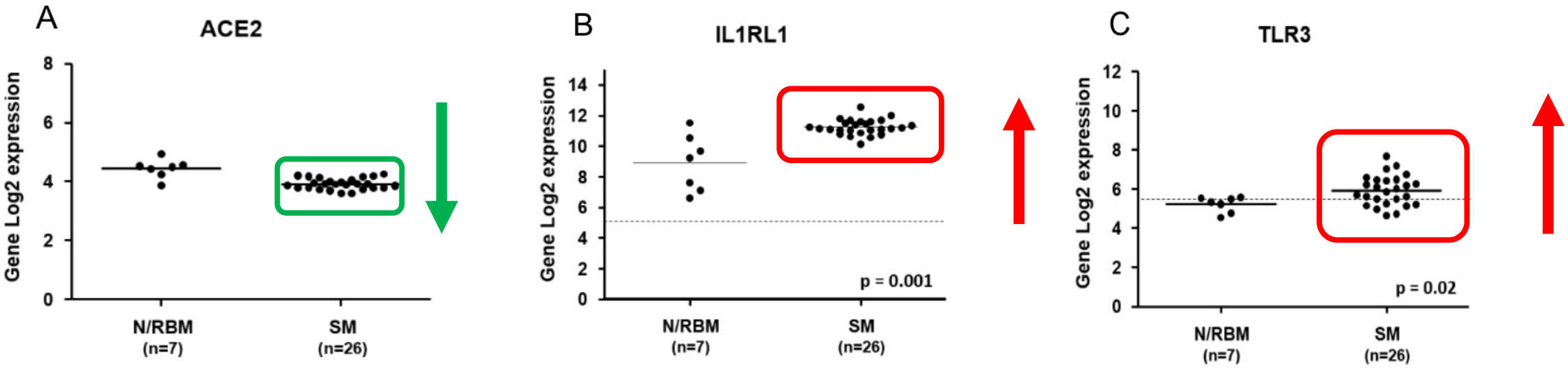
Gene expression of ACE2, TLR3, and IL1RL1 on highly purified bone marrow mast cells normal/reactive N/RBM (n=7) and systemic mastocytosis SM patients (n=26)



Alberto Orfao 2020

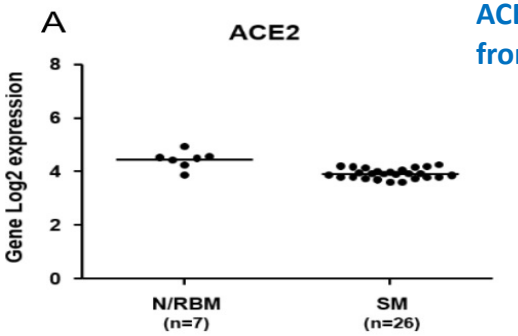
Covid19 mRNA Vaccines Hypersensitivity

- Anaphylaxis is rare (1/100.000-200.000), NO fatalities from hypersensitivity/anaphylaxis
- Females are more affected (90% of cases)
- Epinephrine is the ONLY treatment
- Tryptase should be obtained
- Skin testing: PEG, polysorbate, vaccine
- BAT testing
- No contraindications for vaccination due to previous allergies, anaphylaxis or mast cell activation disorders
- Role of pre-medications
- Large local reactions do not recur

mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis

Tiago Azenha Rama, DMD, MD[a,b]
André Moreira, MD, PhD[a,b,c]
Mariana Castells, MD, PhD[d]

JACI March 2021



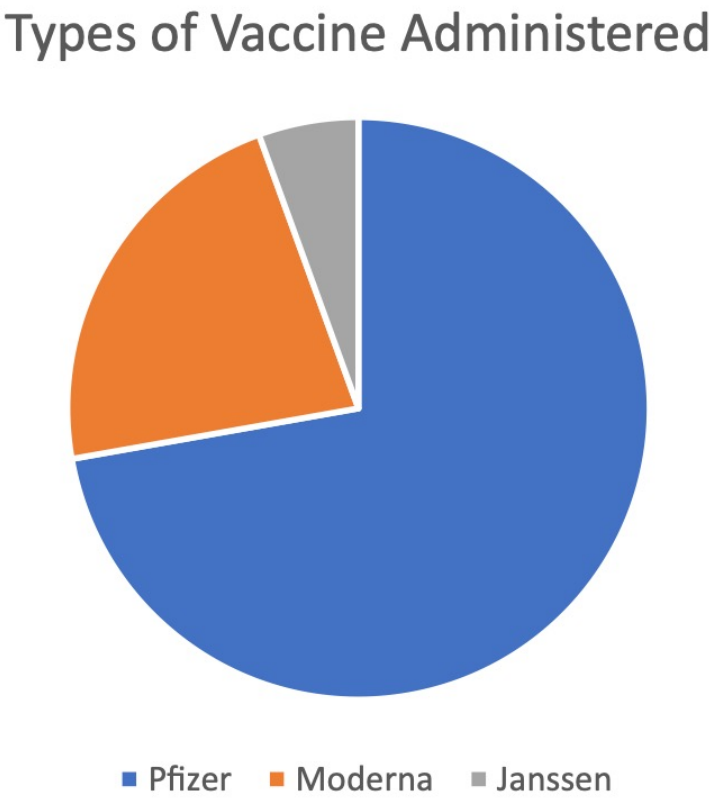
ACE2 receptor absent from BM mast cells
Giannetti et al 2021

Safety of COVID-19 vaccination in patients with mastocytosis and monoclonal mast cell activation syndrome

Rayan Kaakati, MD[a,*], Dilawar Khokhar, MD[b,*], a
Cem Akin, MD, PhD[b]

TABLE I. Demographic characteristics of cohort

Characteristic	Patients, n
Cutaneous mastocytosis	3
Indolent systemic mastocytosis	11
Systemic mastocytosis with an associated hematologic neoplasm	2
Monoclonal mast cell activation syndrome	1
Mastocytosis in skin	1
Sex	
Female	10
Male	8
Age range, y	38-83
Race	
White	17
Middle Eastern	1
Tryptase range, ng/mL	2-136
Atopic comorbid condition	
Allergic rhinitis	6
Asthma	5
Atopic dermatitis	2
History of anaphylaxis	4
Reported allergies	
Drug allergy	10
Contrast	1
Venom	4
Food	1



International Archives of Allergy and Immunology

Position Paper

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Definitions, Criteria and Global Classification of Mast Cell Disorders with Special Reference to Mast Cell Activation Syndromes: A Consensus Proposal

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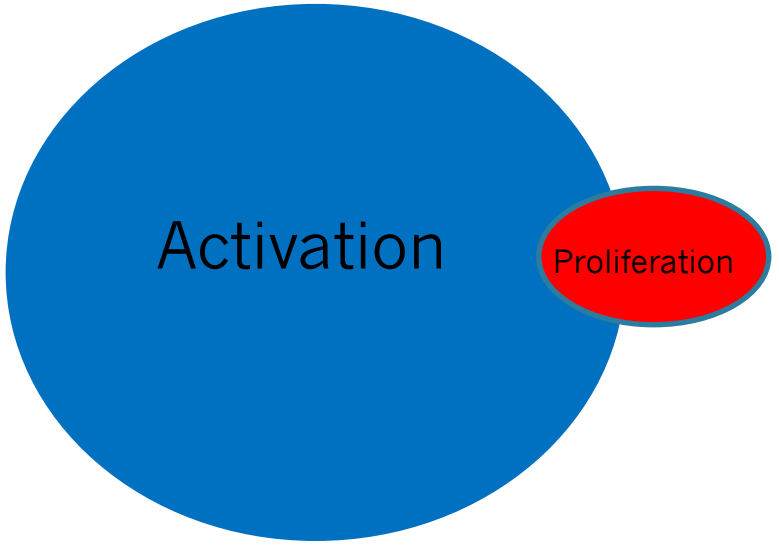


Table 4. Classification of MCASs

Category and variants	Proposed criteria
Primary MCAS Mastocytosis (Mono)clonal MCAS	MCA criteria fulfilled and MC (mono)clonality proven (CD25+ MCs and/or *KIT* D816V)[1]
Secondary MCAS Allergy Other underlying disorder[2]	MCA criteria fulfilled and criteria for the diagnosis of allergy or other diseases that can produce MCA fulfilled as well
Idiopathic MCAS[3]	MCA criteria fulfilled, but no disease that could lead to MCA diagnosed

[1] CD25+ MCs plus *KIT* D816V detectable, or *KIT* D816V detectable, but MCs cannot be demonstrated to express CD25.
[2] Disorders associated with MCA include autoimmune diseases, certain bacterial infections and some adverse drug reactions.
[3] Idiopathic MCAS is a final diagnosis but needs an extensive workup in order to exclude all potential underlying conditions and disorders. Idiopathic and secondary MCA episodes may occur at different time points in the same patient.

Mast Cells: Mediators and Related Symptoms

Table 1 Mast cell mediators and related symptoms

	Mediator(s)	Measured in mastocytosis
Systemic		
Vasodilation/hypotension	Histamine	+
	Prostaglandin D2	+
Hypertension	Chymase	–
Fatigue/cachexia/weight loss	TNF-α	+
Fever	IL-6	+
	IL-1	–
Fibrosis	IL-1	–
	IL-13	–
	TGF-β	–
Skin		
Flushing	Histamine	+
	Prostaglandin D2	+
Urticaria/angioedema	Histamine	+
	Prostaglandin D2	+
	Leukotriene C4	–
Gastrointestinal		
Abdominal pain	Histamine	+
Peptic		
Colic		
Diarrhea	Histamine	+
Malabsorption		
Bone		
Bone pain		
Osteoporosis/osteopenia	IL-6	+
	Heparin	–
	Tryptase	+
	TGF-β	–
Central nervous system		
Mixed CNS syndrome	Prostaglandin D2	+
	Histamine	+

Mast Cell Mediator Related Symptoms

- **Histamine:**
  - Pruritus, urticaria, gastric hypersecretion, bronchoconstriction
  - Increased vasopermeability and systemic hypotension
- **Heparin:**
  - Local anticoagulation and osteoporosis

- **Proteases:**
  - Tryptase: Fibrinogen degradation, stimulation of fibroblast proliferation
  - Chymases: Activation of procollagenases and tissue remodeling
  - Carboxypeptidase A

- **Cysteinyl Leukotrienes**:
  - Increased vasopermeability, vasodilation, bronchoconstriction
  - LTD4, LTC4, LTE4

Castells M , Austen KF, 2002

Mast Cell Mediators and their Effects

Castells and Austen 2002

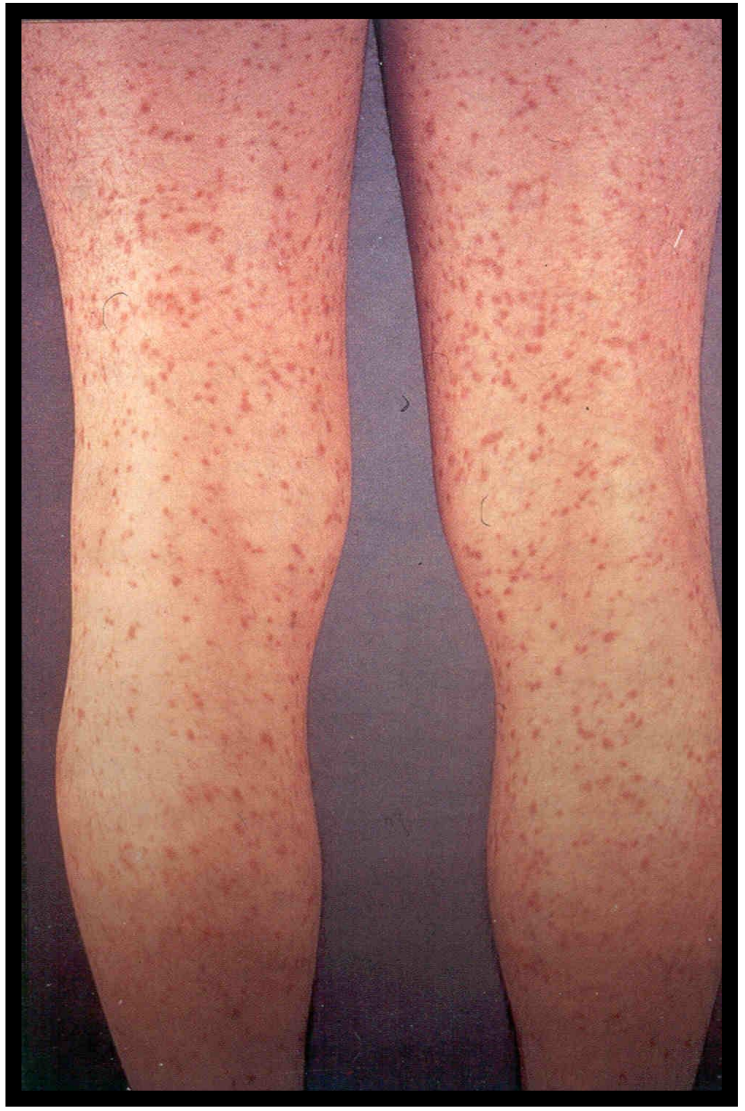
- **Prostaglandins (PGD2):**
  - Vasodilation, bronchoconstriction
  - flushing
  - CNS symptoms
- **Platelet-activating Factor**:
  - Increased Vasopermeability, vasodilation
- **Cytokines:**
  - TNFα: Activation of vascular endothelial cells, cachexia
  - TGFβ: Fibrosis
  - NGF
  - IL-6; Bone remodeling
- **Growth Factors:**
  - IL-3: Mast cell growth
  - IL-5: Eosinophilia

The New York Times Magazine

“Mommy, I am scared, are you okay?”

- The mother, a 32 y/o, was lying unconscious in a public bathroom in a pool of bloody stool after feeling, hot, dizzy and a fluttering heart.

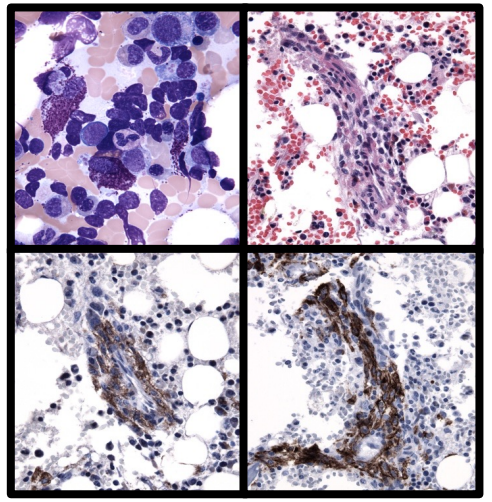
- She told the ER doctors that her only medical problems were panic attacks, flushing and a **rash** that she had for over 10 years. She was told they were freckles.



Case Records of the Massachusetts General Hospital

- Male 33 runner Boston Marathon
- Joint pain 800 mg Ibuprofen
- Flushing, hypotension, SOB, intubation
- **Tryptase >2000 ng/ml**

- Symptoms : flushing, chronic fatigue, depression, anxiety, bone pain, chest pain (multiple MI r/o)
- PE: few macular lesions in chest (CM)
- BMB: MC aggregates, CD25 +
- Positive c-kit D816V mutation
- **Baseline tryptase: 32 ng/ml**



Systemic Mastocytosis

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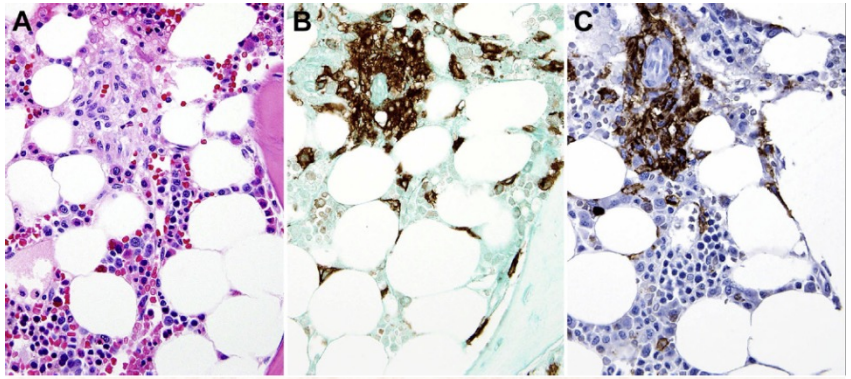
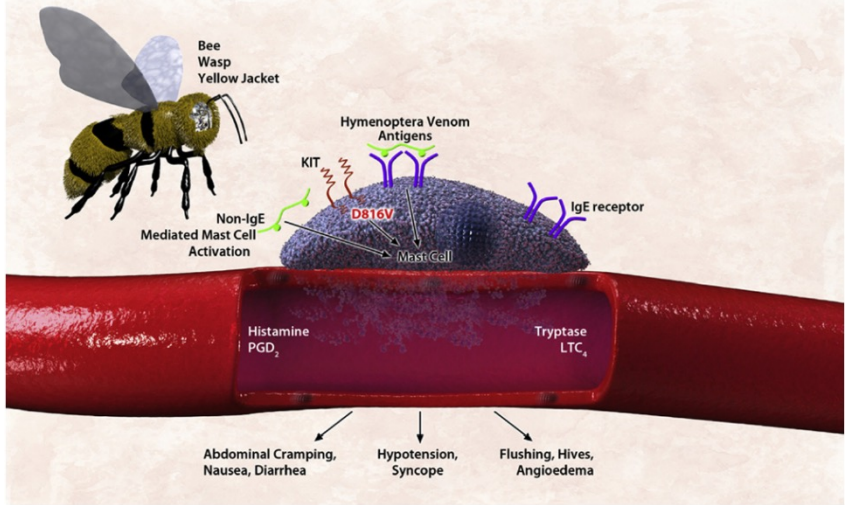
Anaphylaxis After Hymenoptera Sting: Is It Venom Allergy, a Clonal Disorder, or Both?

Mariana C. Castells, MD, PhD, Jason L. Hornick, MD, PhD, and Cem Akin, MD, PhD *Boston, Mass*

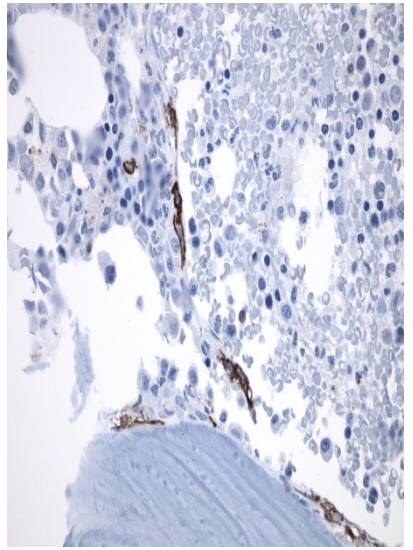
A 47-year-old man presented with loss of consciousness 5 minutes after being stung by a yellow jacket in his backyard. Epinephrine and fluids were required for resuscitation. Allergy evaluation revealed specific IgE to yellow jacket and honeybee, and the patient was started on venom immunotherapy. He had systemic reactions during buildup and a severe anaphylactic episode requiring 3 doses of intramuscular epinephrine at maintenance doses. Immunotherapy was discontinued. Serum tryptase level after 1 such episode was 29 ng/mL, with a baseline level of 25 ng/mL 4 weeks later. The physical examination was unremarkable including no skin lesions of cutaneous mastocytosis. Because of elevated baseline tryptase level, a bone marrow biopsy was performed, which revealed multifocal dense infiltrates of mast cells. A diagnosis of systemic mastocytosis was made. The patient was treated with omalizumab and was able to tolerate immunotherapy and is currently maintained on lifelong immunotherapy. He was restung in the field and has not had anaphylaxis. (J Allergy Clin Immunol Pract 2015;3:350-5)

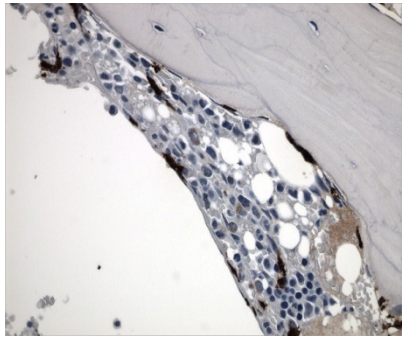


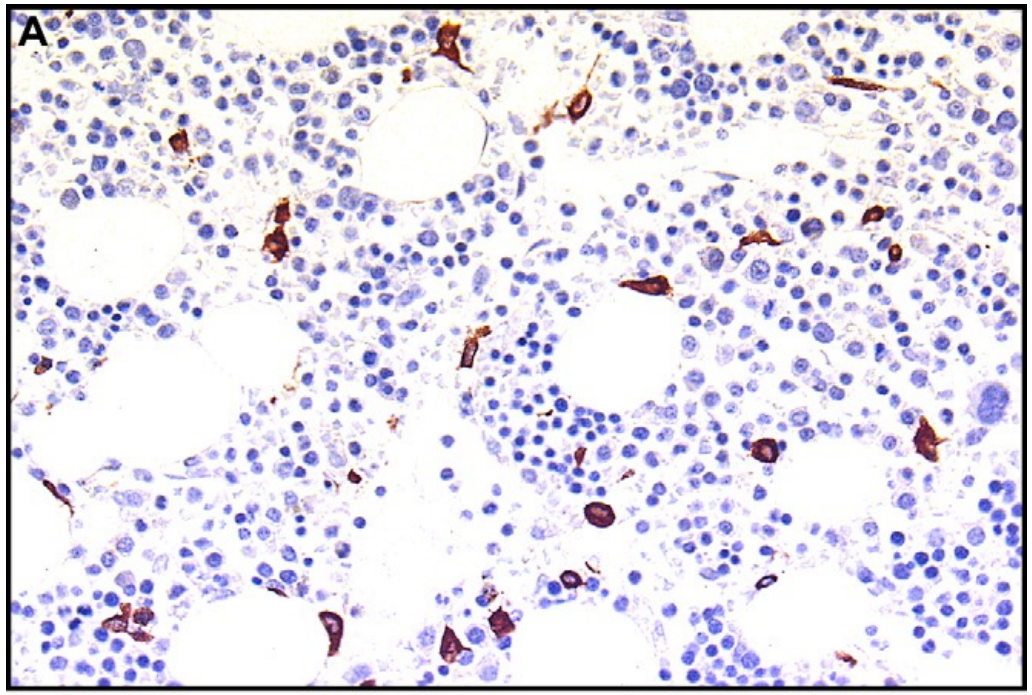


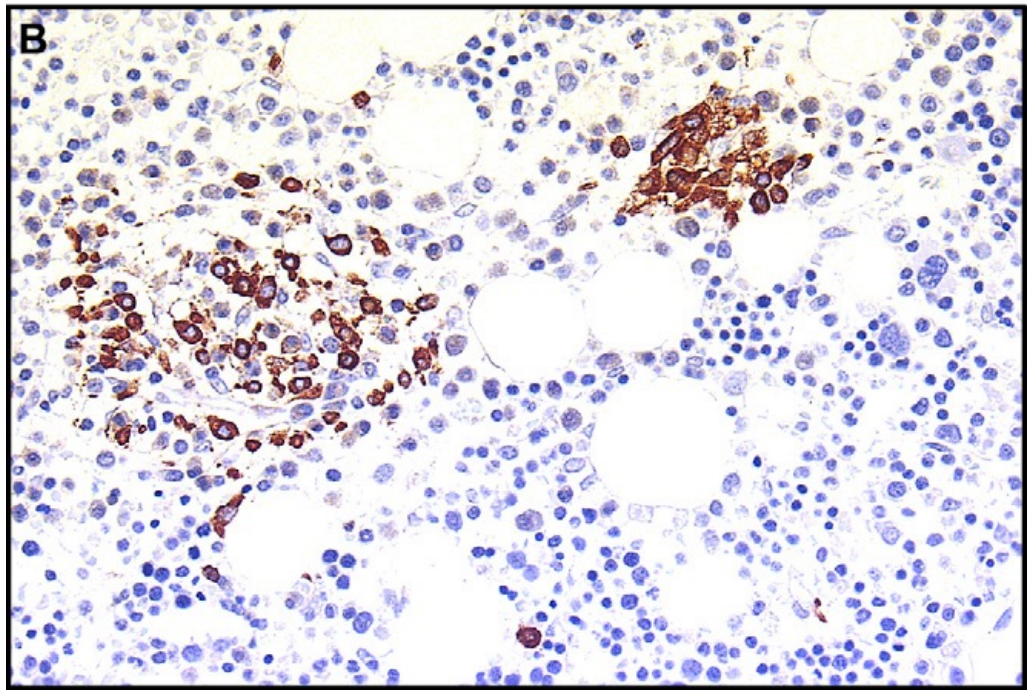
Anaphylaxis During Immunotherapy

- 44 y/o female: seasonal rhinitis ST + grasses, weeds,
- IT: burning hands and feet, chest pressure, lightheadedness epinephrine, IT discontinued
- Severe cramping, abdominal pain, nausea, vomiting, dizzyness, feet and hand burning and feeling of impending doom, no hives
- ER: 60/30 multiple epinephrine
    - **Tryptase: 8.75 ng/ml total, <1 ng/ml mature**
    - **PB : c-kit D816V mutation**
    - **IgE : 18 IU/ml; Specific IgE foods (-)**
    - **BMB: no MC aggregates, spindle MC, Positive CD25 MC**









Monoclonal Mast Cell Activation Disorder

Systemic Mastocytosis

Akin, Metcalfe, Valent JACI 2010

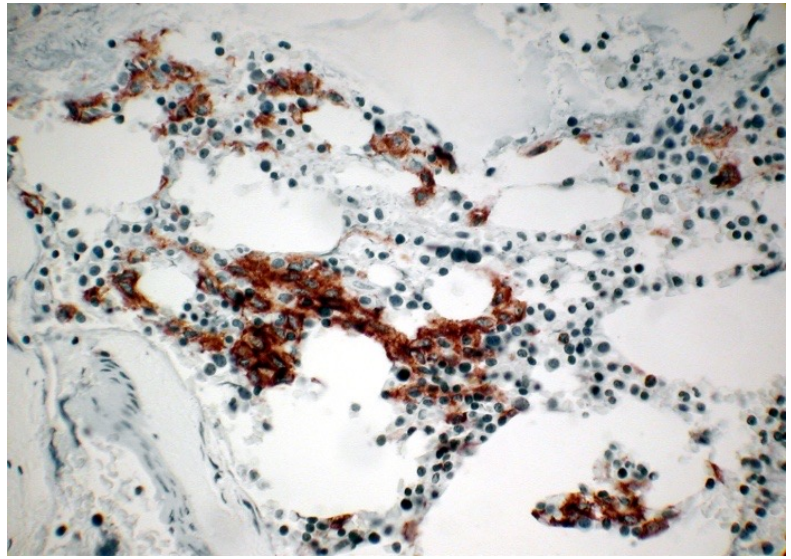
Primary Clonal Mast Cell Diseases

TABLE I. Classification of mastocytosis[4]

Cutaneous mastocytosis
Systemic mastocytosis
ISM
Systemic mastocytosis associated with a hematologic disorder
Aggressive systemic mastocytosis
Mast cell leukemia
Mast cell sarcoma
Extracutaneous mastocytosis

TABLE II. Diagnostic criteria of systemic mastocytosis[4]: The major and at least 1 minor, or 3 minor criteria are needed

Major
Multifocal mast cell aggregates (>15 mast cells per aggregate) in an extracutaneous tissue (often bone marrow) biopsy
Minor
Abnormal mast cell morphology (spindle-shaped, hypogranulated)
Aberrant CD2 or CD25 expression by mast cells
Codon 816 KIT mutation in blood or lesional tissue
Baseline tryptase level >20 ng/mL (not valid in patients with other hematologic disorders)



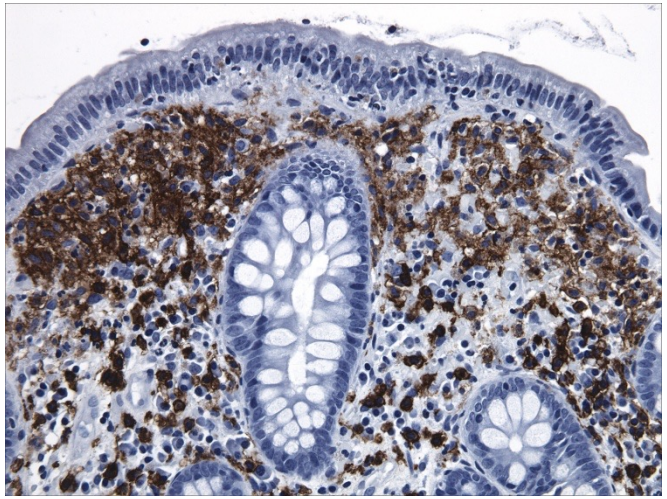
Well differentiated mastocytosis (WDSM)

Alvarez Towse et al 2016

Systemic Mastocytosis without cutaneous involvement and with hymenoptera anaphylaxis

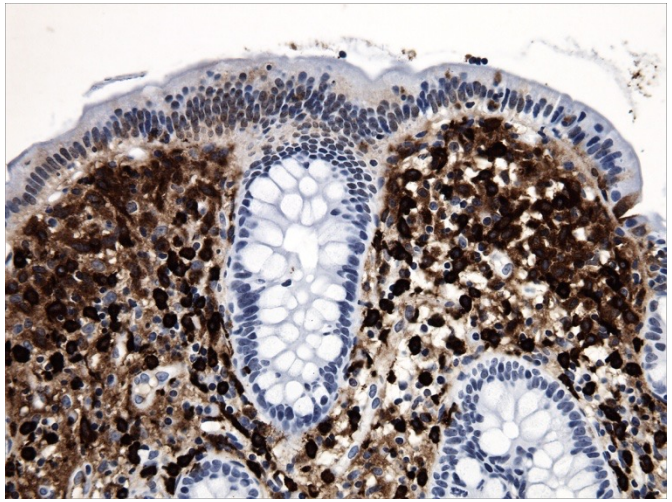
Bonnadona et al 2016

Gastrointestinal Infiltration of Mast Cells: Systemic Mastocytosis

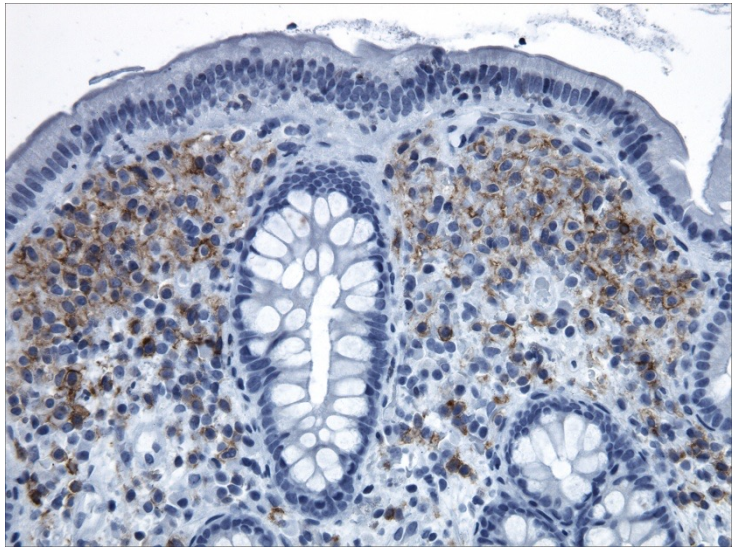


KIT

Tryptase



CD25



A Clinicopathologic Study of 24 Cases of Systemic Mastocytosis Involving the Gastrointestinal Tract and Assessment of Mucosal Mast Cell Density in Irritable Bowel Syndrome and Asymptomatic Patients

Leona A. Doyle, MD*, **Golrokh J. Sepehr, MD***, **Matthew J. Hamilton, MD†,‡, Cem Akin, MD, PhD†,‡, Mariana C. Castells, MD†,‡,** and **Jason L. Hornick, MD ,PhD** **2014**

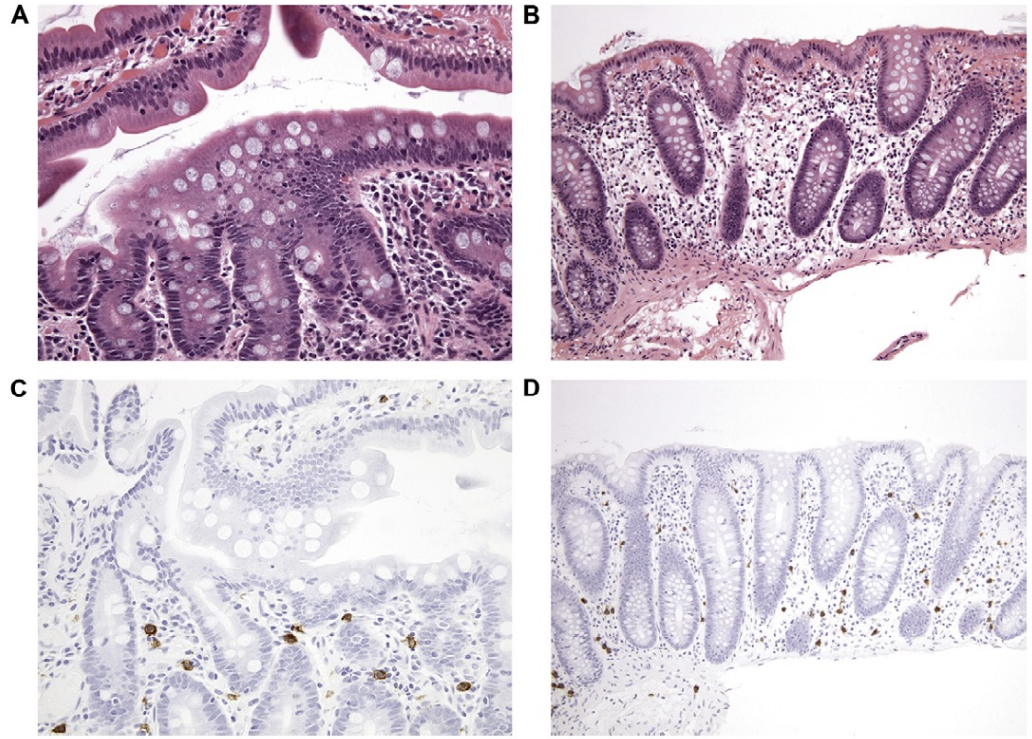
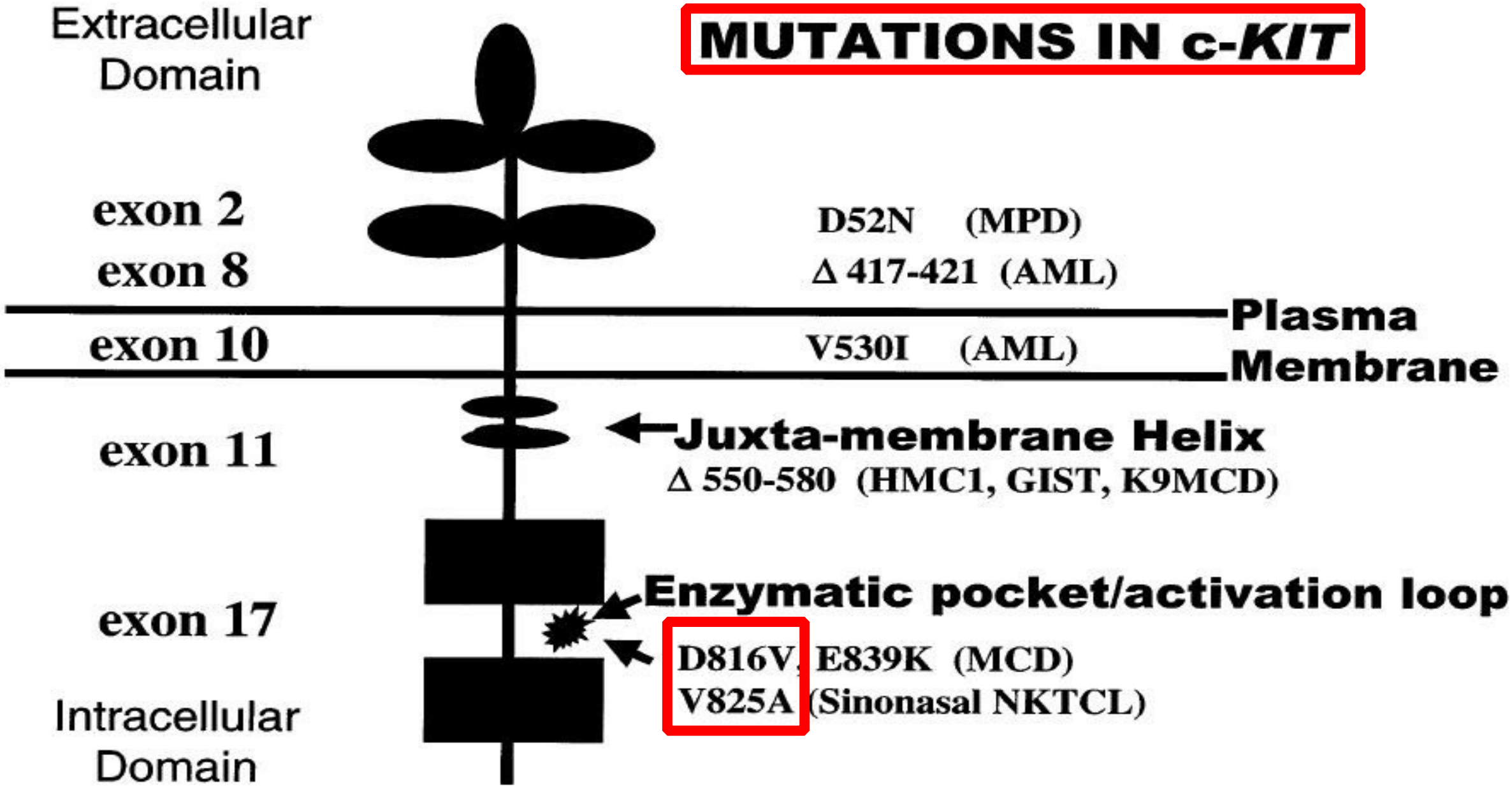


TABLE IV. Mean number of MCs at each site

Site of biopsy	No. of patients	Mean/hpf (normal)*	Range (normal)*
Stomach	7	17 (13)	14-28 (5-21)
Duodenum	7	23 (27)	18-26 (4-51)
Left colon	5	20 (21)	15-27 (10-31)
Right colon	4	17 (21)	12-18 (10-31)

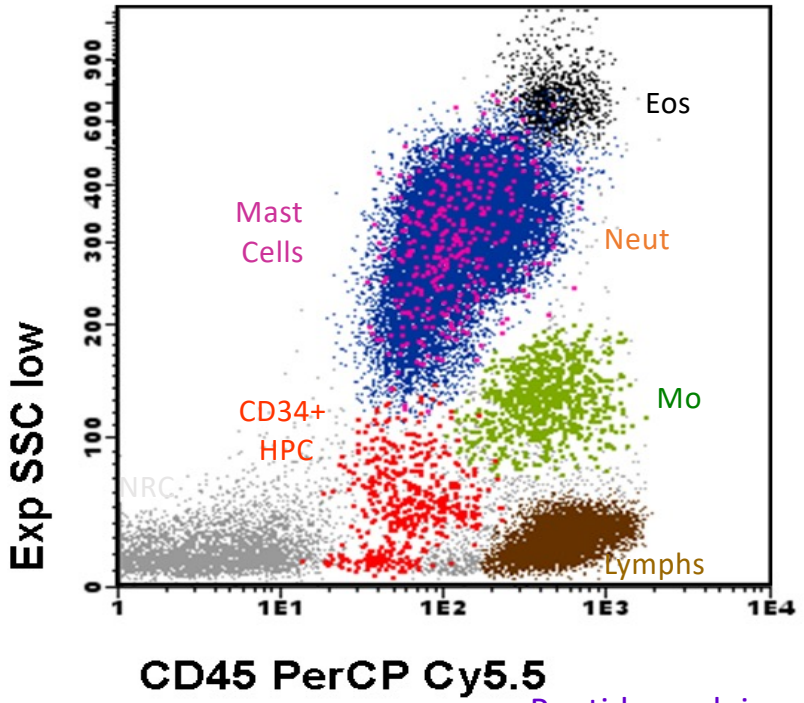
*Data from Hahn and Hornick.[18]



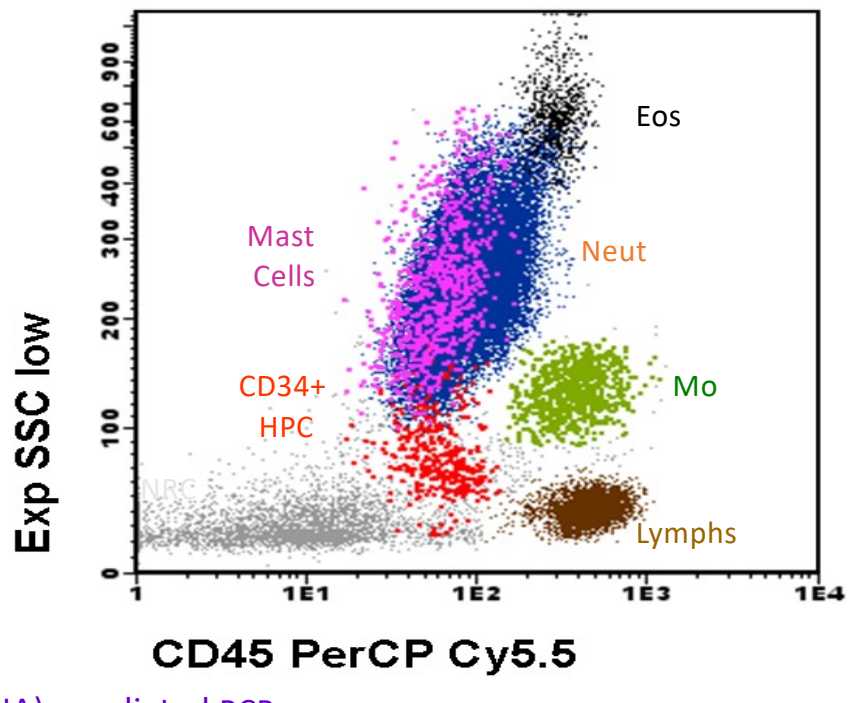
From: Longley, B.J. *et. al., Leukemia Research 25:* 571-576, 2001

Different Patterns of KIT Mutation in Indolent Systemic Mastocytosis

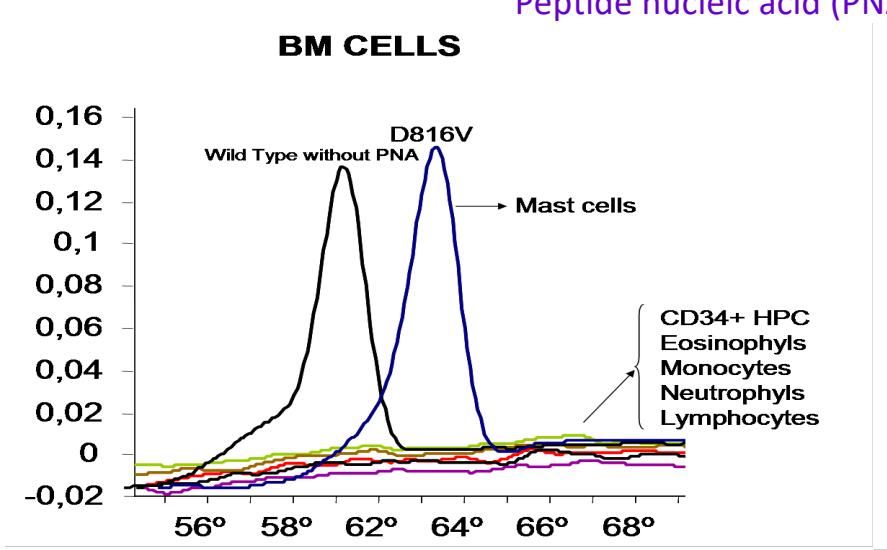
Case 1

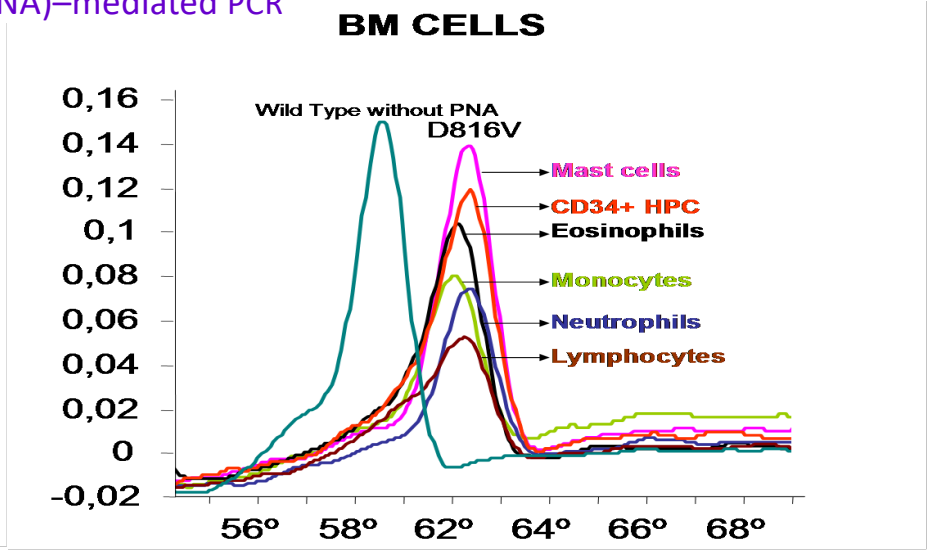


Case 2



Peptide nucleic acid (PNA)–mediated PCR

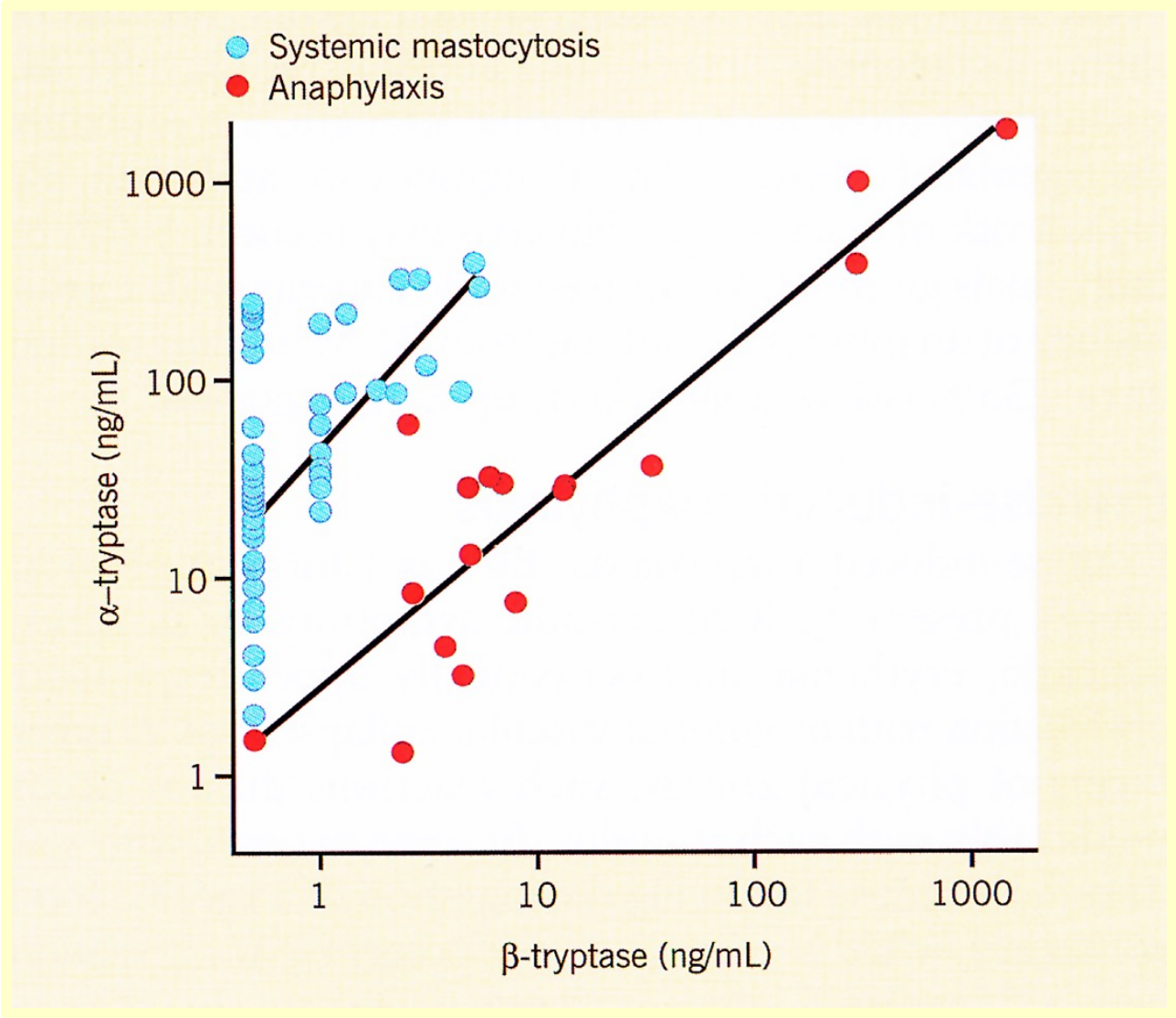




Escribano et al 2009

Tryptase Levels in Anaphylaxis and Systemic Mastocytosis

Schwartz, NEJM1987



Task force report

Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology

JACI 2016

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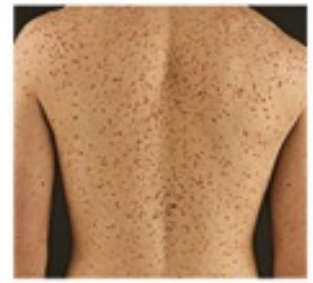
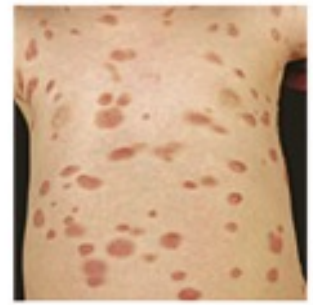
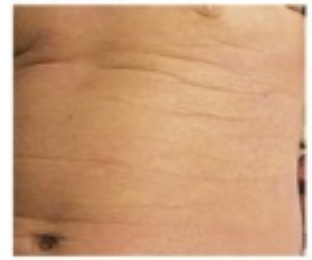
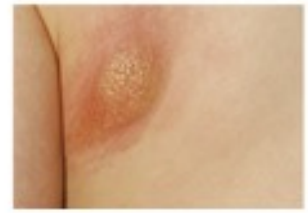
Cologne, Luebeck, Munich, Mannheim, and Berlin, Germany, Salamanca, Toledo, and Madrid, Spain, Norwich and London, United Kingdom, Bethesda, Md, Odense, Denmark, Gdansk, Poland, Boston, Mass, Groningen, The Netherlands, Verona and Salerno, Italy, Aarau, Switzerland, Rochester, Minn, Stanford, Calif, Paris and Cachan, France, Albuquerque, NM, Istanbul, Turkey, Stockholm, Sweden, Vienna, Austria, and Richmond, Va

Subforms	Variants	Typical manifestations
Maculopapular cutaneous mastocytosis (syn. urticaria pigmentosa)	Monomorphic	
	Polymorphic	
Diffuse cutaneous mastocytosis		
Cutaneous mastocytoma		

Darier’s Sign

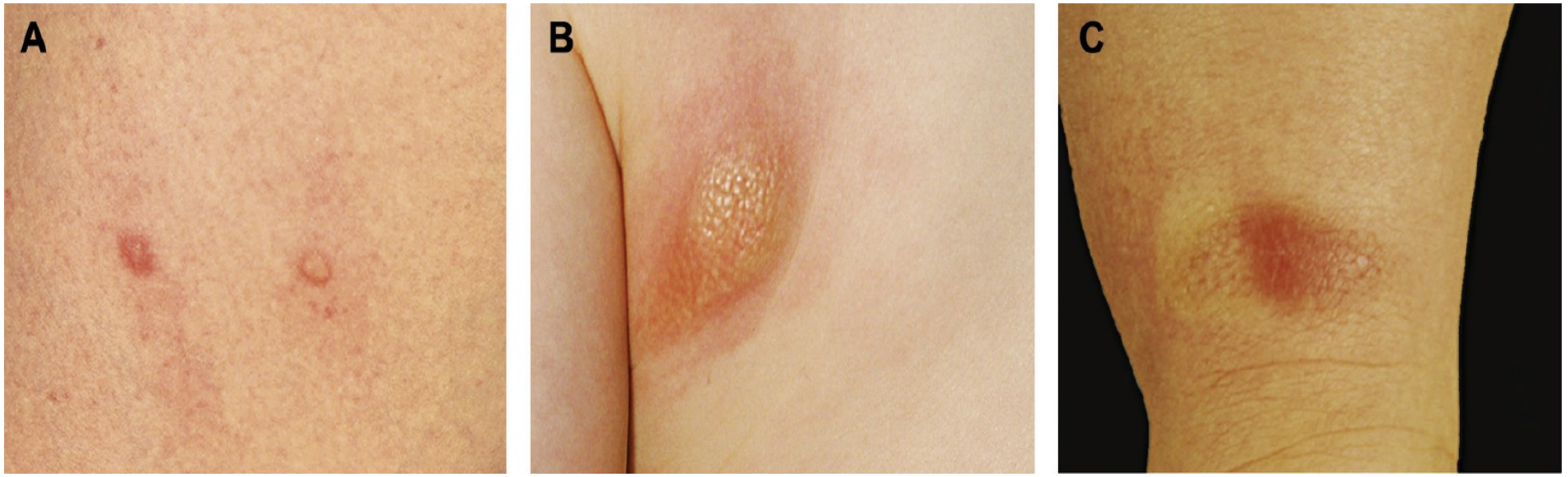


FIG 3. Darier’s sign. A-C, A wheal-and-flare reaction develops upon stroking of a CM lesion with a tongue spatula. Darier’s sign is a highly specific diagnostic feature of CM.

Cutaneous manifestations in patients with Mastocytosis:

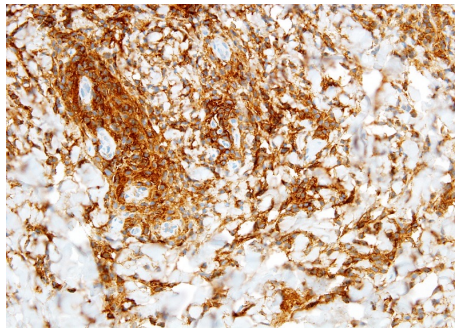
Consensus report European Competence Network on Mastocytosis
American Academy of Asthma Allergy and Immunology
European Academy of Allergy and Clinical Immunology 2016

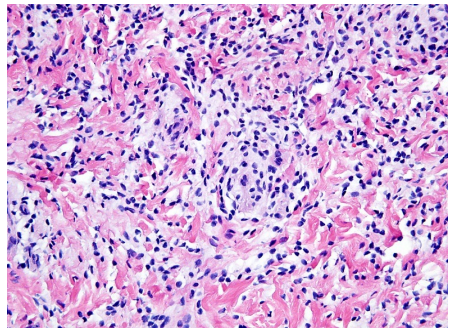
TABLE I. Characteristics of typical adulthood-onset and typical childhood-onset mastocytosis

Parameter	Adulthood-onset mastocytosis	Childhood-onset mastocytosis
Most frequent category of mastocytosis	ISM	Cutaneous mastocytosis
Typical course of the disease	Chronic	Temporary
Frequency of anaphylaxis (%)	50	<10
Typical tryptase level (μg/L)	>20	<20
Typical location of *KIT* mutation	Exon 17, most frequently *KIT* D816V	Exon 8, 9, 11, or 17 or absent
Most frequent type of cutaneous lesions	Maculopapular	Maculopapular
Typical morphology of maculopapular lesions	Monomorphic	Polymorphic
Typical size of maculopapular lesions	Small	Large
Typical distribution of maculopapular lesions	Thigh, trunk	Trunk, head, extremities

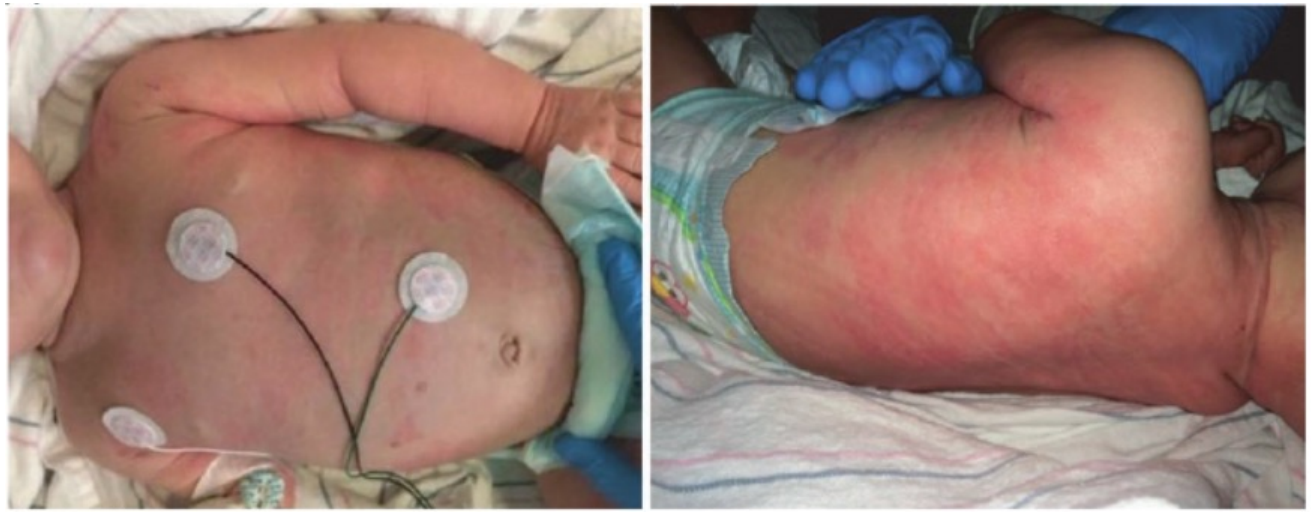
Diffuse cutaneous mastocytosis with novel somatic KIT mutation K509I and association with tuberous sclerosis

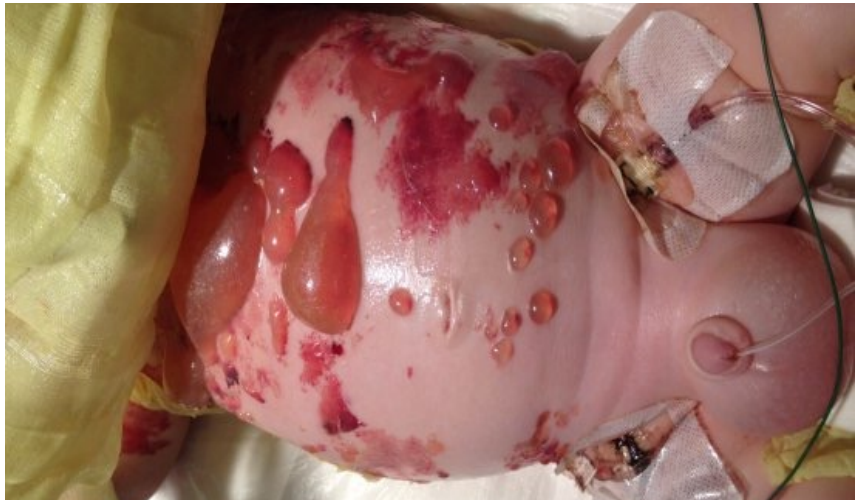
Iris M. Otani[1] | Ryan W. Carroll[2] | Phoebe Yager[2] | Daniela Kroshinsky[3] | Sarah Murphy[2] | Jason L. Hornick[4] | Cem Akin[5,6] | Mariana Castells[5,6] | Jolan E. Walter[7,8]





4-month-old boy with fever, viral disease, skin blistering, seizure (vancomycin), ARDS, cardiac arrest





Mast Cell Activation Disorders

Mast Cell Activation Syndrome (MCAS)

Diagnostic criteria

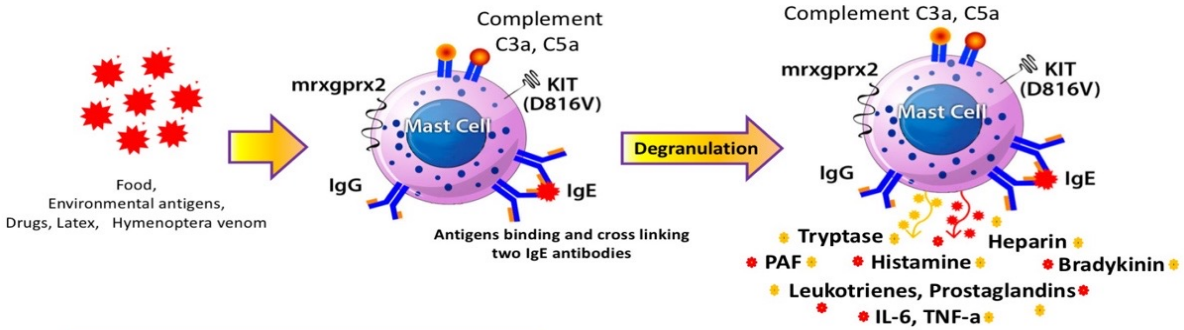
- 1. Episodic multisystem symptoms consistent with mast cell activation
- 2. Appropriate response to medications targeting mast cell activation
- 3. Documented increase in validated markers of mast cell activation systemically during a symptomatic period

Symptoms (two or more organs):

- **SKIN**: Itching, Rash, Flushing, Hives.
- **Gastro-Intestinal (GI):** Abdominal pain, Diarrhea, Bloating, Nausea.
- **Respiratory**: Closing Throat, Chest Tightness, Wheezing, Shortness of breath.
- **Central Nervous System**: Brain Fog, Short Memory Span or Inability to Concentrate.
- **Cardiovascular**: Dizziness, Presyncope or Syncope
- **Bone:** Pain, Osteopenia, Osteoporosis, Fractures.
- **Others**: Joints and muscles pain, Fatigue.
- **Anaphylaxis.**

Triggers

- Foods, e.g. Chocolate, spicy foods.
- Drugs, e.g. NSAIDs, opioids, vancomycin, others)
- Hymenoptera Venom
- Alcohol
- Stress, emotions, anxiety, exercise
- Changes in temperature
- Heat
- Surgery
- Vaccines
- RCM



Hereditary Alpha Tryptasemia

Clonal MCAS
Mastocytosis
(↑ Mast cell number)

Cutaneous Mastocytosis
(Aggregates of MC in the Skin)

- Maculopapular (CM) = urticaria pigmentosa
  - Polymorphic
  - Monomorphic
- Diffuse (DCM)
- Localized mastocytoma of skin
- TMPE

Monoclonal Mast Cell Activation Syndrome
(MMAS)

Systemic Mastocytosis
(Aggregates of MC in the Bone Marrow)

WHO Criteria

- **Major:**
  - Aggregates of >15 MC in BM or GI biopsy.
- **Minor**
  - Spindle mast cell on BM or GI.
  - Tryptase >20ng/ml.
  - c- Kit 816V Mutation.
  - CD-25 positive mast cells

Subtypes SM:

- Indolent (ISM)
- Smoldering (SSM)
- SM with an associated hematologic (non-MC lineage) neoplasm (SM with AHN)
- Aggressive SM(ASM)
- MC leukemia (MCL).
- MC sarcoma

Non Clonal MCAS
(↑Activation mast cells)

1. Symptoms of MCA in 2 or more organs.
2. ↑ Mediators (Tryptase, Urine-histamine, prostaglandins, Leukotrienes).
3. >50% response to mediators controller medications
4. Absence of other diseases.
5. In case any of those diseases POTS, EDS, Allergies, Autoimmune diseases, secondary MCAS.

Mast Cell Activation Symptoms in Systemic Mastocytosis

- 30 y/o male severe osteoporosis of both hips/bilateral prosthesis
- **Symptoms** : Intermittent **diarrhea, inability to concentrate, mental fogginess, flushing, unprovoked anaphylaxis**
- Tryptase: 60 ng/ml
- Hip biopsy: aggregates of >50 mast cells, spindle shaped, CD25 +

Diagnosis: Indolent Systemic Mastocytosis

22 y/o with asthma, allergies, anaphylaxis, abdominal pain, flushing Hereditary Alpha Tryptasemia

- HPI: since age 12 severe asthma, allergies, abdominal pain, bloating, diarrhea, flushing, hives CIU, unprovoked anaphylaxis, dizziness, fatigue, hypermobility, joint pain. **Cannot work a steady job due to HR and dizziness/presyncope during prolonged standing (> 10 min). Musician (song named Tryptase)**
- PMH: Orthostatic cerebral hypoperfusion syndrome **(OCHOS)/POTS**, **small fiber neuropathy and EDS**,
- FH: mother and brother with **POTS**
- Labs : **Tilt test +, Biopsy + : small fiber neuropathy**, Orthostatic cerebral blood flow velocity test: "abnormally reduced without the presence of orthostatic hypotension or hyperventilation, indicating cerebral hypoperfusion on standing. The mechanisms leading to **OCHOS may include abnormal cerebral vasoconstriction."**

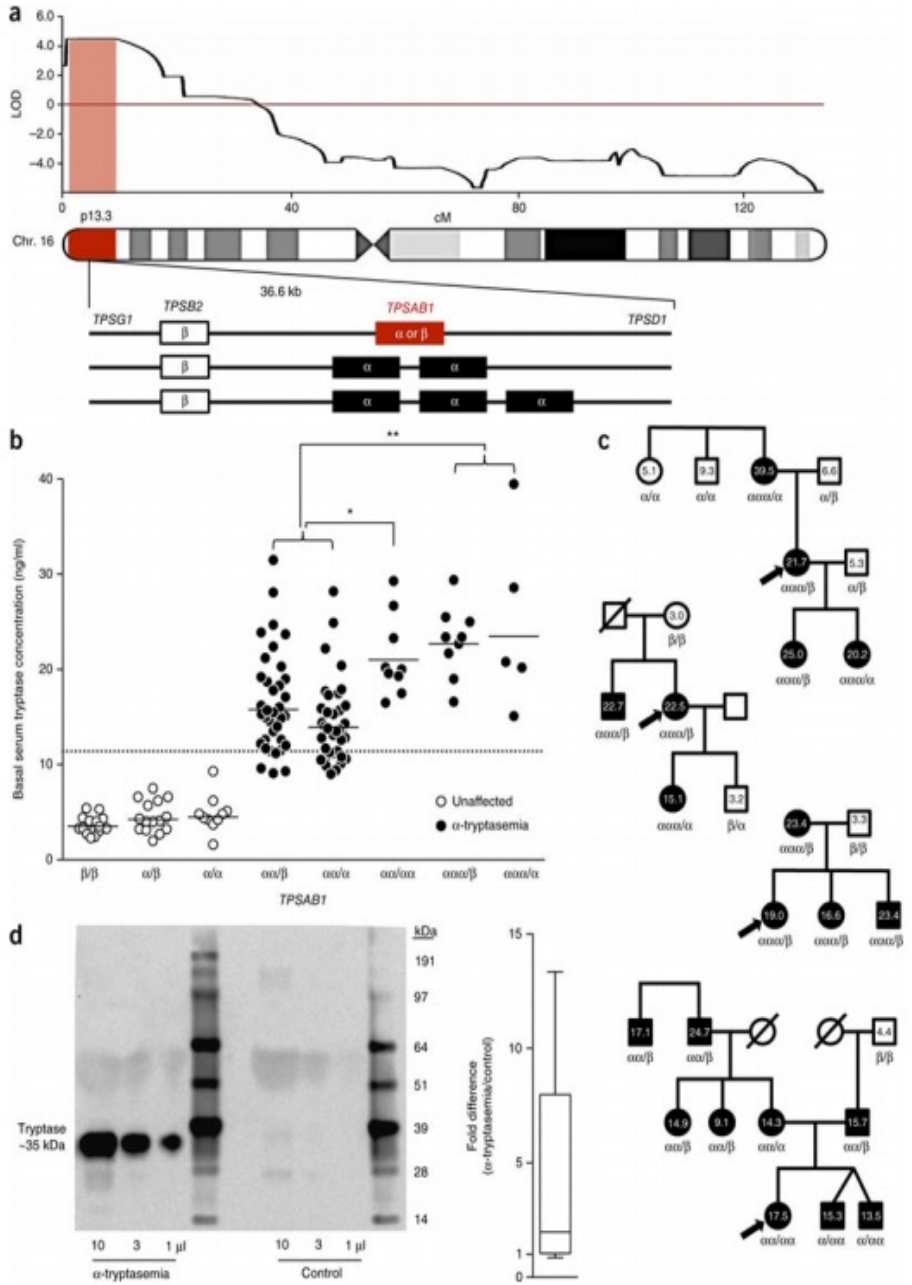
- **Tryptase: 18 ng/ml**
- **IgE 264 IU/ml , spIgE + wheat, peanut, soy, scallops, cat, dust mites, pollen**

Hereditary Alpha Tryptasemia

Lyons et al Nature Genetics 2016

Clinical features and gene-dose effects in hereditary α-tryptasemia syndrome

	Hereditary α-tryptasemia syndrome (α)		*TPSAB1* duplication (αα)		*TPSAB1* triplication (ααα)		*P* value[a]
Serum tryptase, ng/ml Median Interquartile range	15.9 12.6–20.7		14.3 11.6–17.8		23.4 19.8–26.4		<0.0001
Manifestation	*n*	%	*n*	%	*n*	%	*P* value[a]
Systemic venom reaction[b]	15/96	16	11/73	15	4/15	27	NS
Flushing/pruritus	49/96	51	**33/73**	**45**	**12/15**	**80**	**0.022**
IBS (Rome III)	34/70	49	26/53	49	7/12	58	NS
Chronic gastroesophageal reflux symptoms	62/96	65	**42/73**	**49**	**15/15**	**100**	**0.001**
Congenital skeletal abnormality[c]	25/96	26	**14/73**	**19**	**8/15**	**53**	**0.009**
Retained primary dentition	20/96	21	**12/73**	**16**	**7/15**	**47**	**0.016**
Hypermobility (Beighton score ≥4)[d]	14/50	28	11/30	37	3/13	23	NS
COMPASS 31[e]	33/70	47	26/57	46	5/11	45	NS
Positive tilt-table test	11	≥11	6	≥8	4	≥26	ND
Arthralgia	43/96	45	**31/73**	**42**	**11/15**	**73**	**0.045**
Body pain/headache	45/96	47	**32/73**	**44**	**11/15**	**73**	**0.049**
Sleep disruption	37/96	39	**23/73**	**32**	**11/15**	**73**	**0.004**



Heritable risk for severe anaphylaxis associated with increased α-tryptase–encoding germline copy number at *TPSAB1*

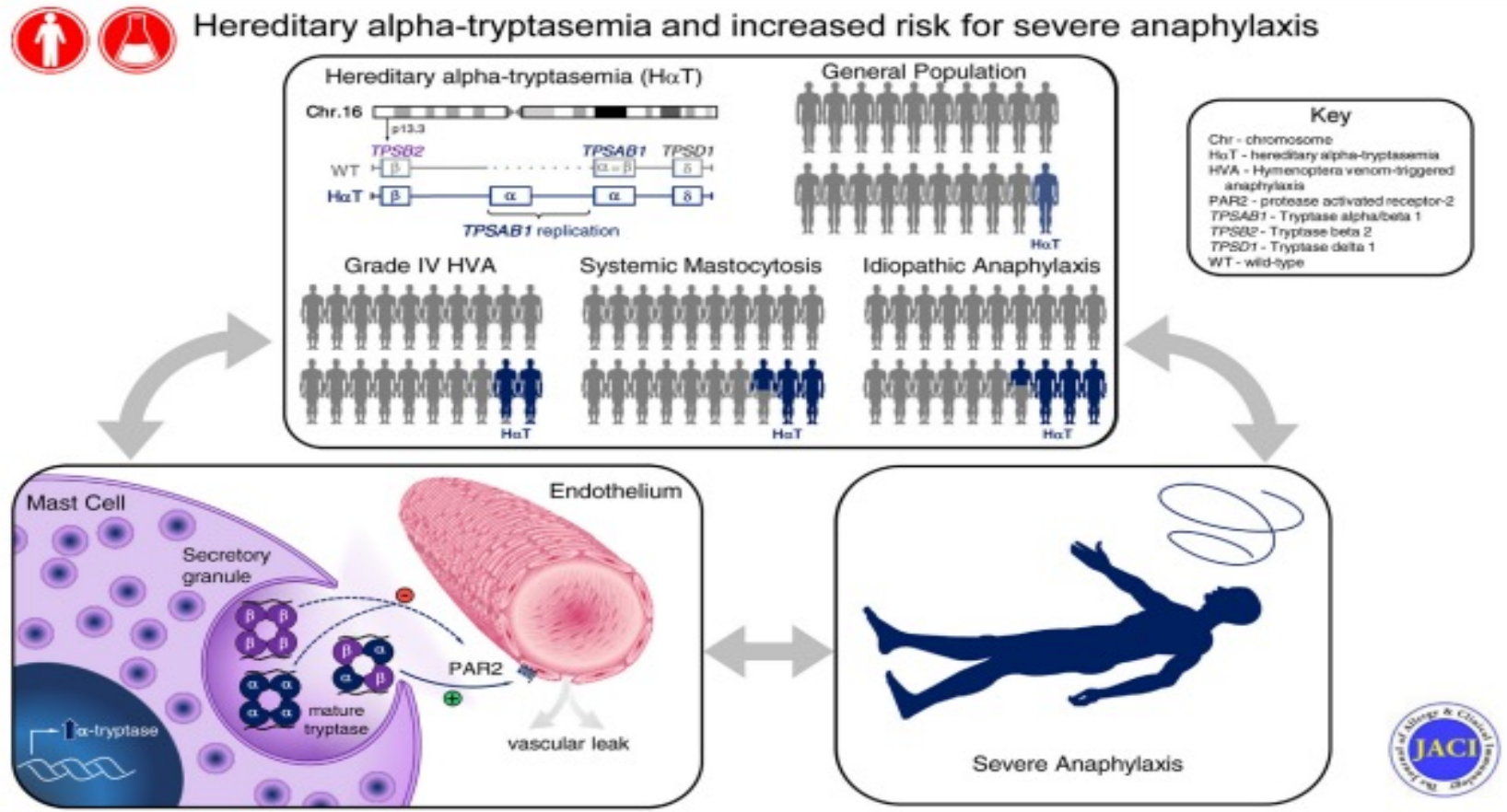
Check for updates

2021

Jonathan J. Lyons, MD,[a] Jack Chovanec, BS,[a] Michael P. O'Connell, PhD,[a] Yihui Liu, PhD,[a] Julij Šelb, MD, PhD,[b] Roberta Zanotti, MD,[c] Yun Bai, PhD,[a] Jiwon Kim, BS,[a] Quang T. Le, PhD,[d] Tom DiMaggio, ADN,[a] Lawrence B. Schwartz, MD, PhD,[d] Hirsh D. Komarow, MD,[a] Matija Rijavec, PhD,[b] Melody C. Carter, MD,[a] Joshua D. Milner, MD,[e]* Patrizia Bonadonna, MD,[f]* Dean D. Metcalfe, MD,[a]* and Peter Korošec, PhD[b]*

Bethesda, Md, Golnik, Slovenia, Verona, Italy, Richmond, Va, and New York, NY

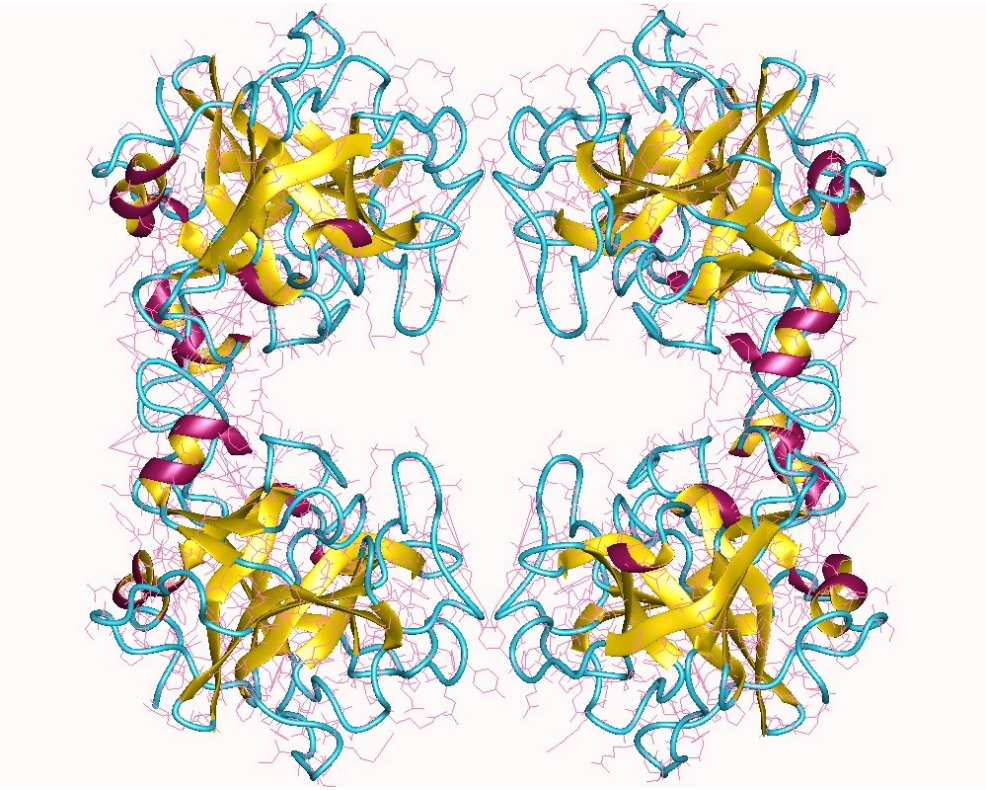
- HαT is the common cause of elevated BST level in Western populations and the first common heritable genetic modifier of anaphylaxis to be described.
- Having concomitant clonal mast cell disease and HαT is associated with greater likelihood of severe anaphylaxis.
- α/β-Tryptase heterotetramers have unique activities that may potentiate immediate hypersensitivity reaction severity.



Is α-tryptase Truly Inactive?

- Mature tryptase tetramer
  - From monomeric protryptase x 4
  - Needs heparin and cathepsins
  - Central pore active site
- Alpha tryptase on its own shows no proteolytic activity

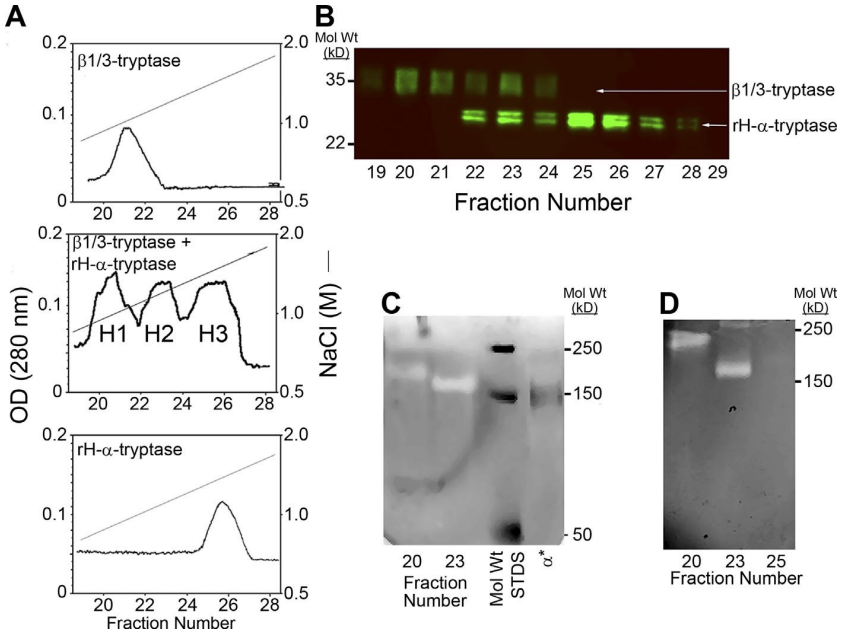
*****So how does increase serum concentration cause disease?**

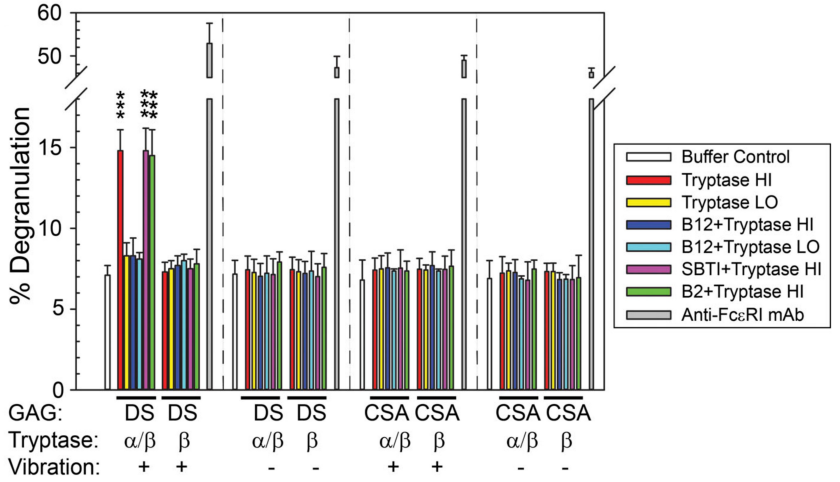


Quang TL, et al. J Exp Med 2019

α/β-Tryptase Heterotetramers Form *in vitro*

Quang TL, et al. J Exp Med 2019



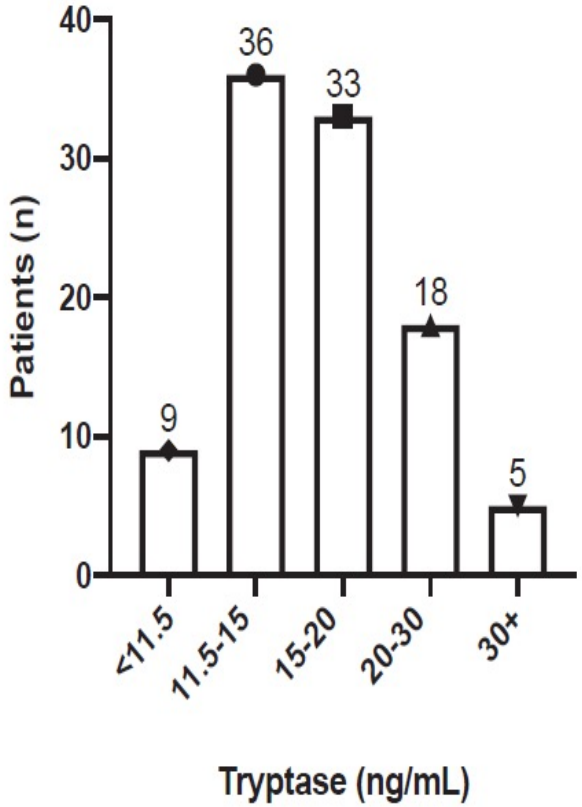


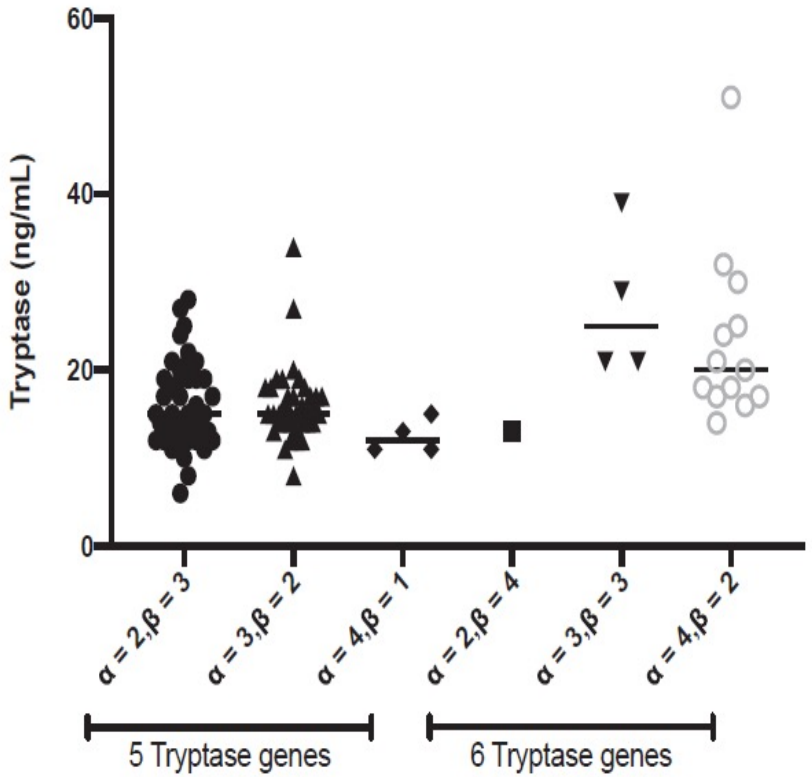
α/β-Tryptase (but not β-tryptase) makes human MCs susceptible to vibration-triggered degranulation

Both α-tryptase and β-tryptase are preferentially expressed by human mast cells, but the purpose of α-tryptase is enigmatic, because its tetramers lack protease activity, whereas β-tryptase tetramers are active proteases. The monogenic disorder called hereditary α-tryptasemia, due to increased α-tryptase gene copies and protein expression, presents with clinical features such as vibratory urticaria and dysautonomia. We show that heterotetramers composed of 2α- and 2β-tryptase protomers (α/β-tryptase) form naturally in individuals who express α-tryptase. α/β-Tryptase, but not homotetramer, activates protease-activated receptor-2 (PAR2), which is expressed on cell types such as smooth muscle, neurons, and endothelium. Also, only α/β-tryptase makes mast cells susceptible to vibration-triggered degranulation by cleaving the α subunit of the EGF-like module–containing mucin-like hormone receptor-like 2 (EMR2) mechanosensory receptor. Allosteric effects of α-tryptase protomers on neighboring β-tryptase protomers likely result in the novel substrate repertoire of α/β-tryptase tetramers that in turn cause some of the clinical features of hereditary α-tryptasemia and of other disorders involving mast cells.

Hereditary alpha-tryptasemia in 101 patients with mast cell activation–related symptomatology including anaphylaxis

Matthew P. Giannetti, MD [*,†]; Emily Weller, BA [*]; Concetta Bormans, PhD [‡]; Peter Novak, MD, PhD [§]; Matthew J. Hamilton, MD [†,‖]; Mariana Castells, MD, PhD [*,†]

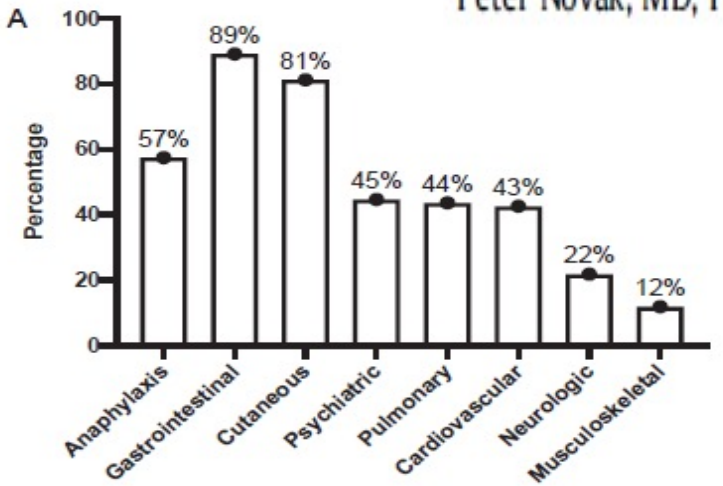


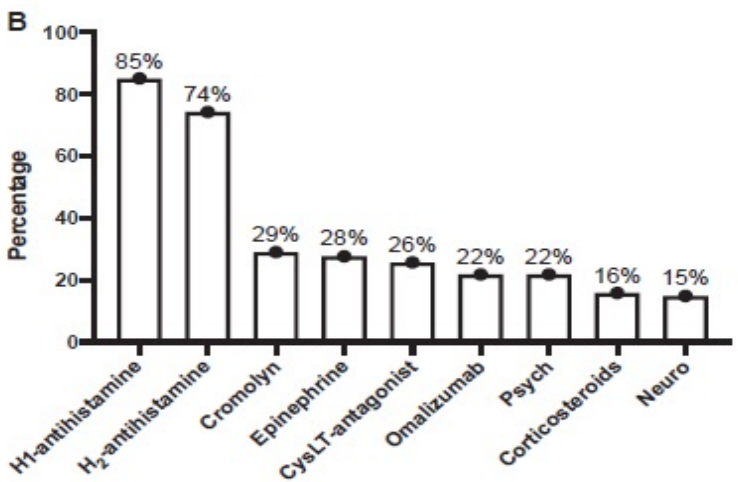


Annals 2021

Hereditary alpha-tryptasemia in 101 patients with mast cell activation–related symptomatology including anaphylaxis

Matthew P. Giannetti, MD[*,†]; Emily Weller, BA[*]; Concetta Bormans, PhD[†]; Peter Novak, MD, PhD[§]; Matthew J. Hamilton, MD[†,‖]; Mariana Castells, MD, PhD[*,†]





Response to Omalizumab

Age	Sex	Genotype	Tryptase	Symptoms	Anaphylaxis	Triggers of anaphylaxis	Improved after omalizumab
77	F	α − 2, β − 3	13.8	S, R	Y	Food	Yes
47	F	α − 4, β − 1	14.6	GI, P, N, S, CV, R, MSK	Y	Drugs Fragrance	No
18	F	α − 2, β − 3	13	GI, S, R	Y	Venom	Yes
64	F	α − 2, β − 3	20.6	GI, R	Y	Drugs	Yes
59	F	α − 2, β − 3	11	GI, S	Y	Food	Yes
33	F	α − 2, β − 3	11.8	GI, P, CV, S, R	N	N/A	Yes
60	F	α − 2, β − 3	25	GI, P, N, S, CV, R	Y	Drugs	Yes
58	F	α − 4, β − 2	14.4	P, S, R	Y	Food Drugs	Yes
46	F	α − 2, β − 3	17	GI, CV, S, R	Y	Drugs	Yes
60	F	α − 3, β − 2	19.1	GI, P, CV, S, R	Y	Drugs	Yes
44	F	α − 4, β − 2	18.1	GI, P, S, N, R	Y	Food Drugs Chemicals Fragrance	Yes
59[a]	F	α − 2, β − 3	14.3	GI, CV, S, R	Y	Drugs	Yes
63	F	α − 3, β − 2	18.1	GI, P, S	Y	Food	Yes
56	M	α − 4, β − 2	30	S	N	N/A	Yes
15	M	α − 3, β − 3	21	GI, P, CV, S, MSK	Y	Drugs	Yes
45	M	α − 3, β − 2	14.0	GI, S	Y	Drugs Food	Yes
72	F	α − 3, β − 2	14.5	GI, CV	Y	Venom	Yes
63	F	α − 2, β − 3	28.4	GI, CV, S, R	N	N/A	Yes
Mean: 52.2	83.3% F		17.7 ± 5.5	S (88.9%) R (66.7%) GI (83.3%)	83.3% with anaphylaxis	Drugs (55.6%)	94.4%

NOTE. Symptom coding: GI (gastrointestinal), S (skin/cutaneous), R (respiratory), P (psychiatric), CV (cardiovascular), N (neurologic), and MSK (musculoskeletal).
Abbreviations: F, female; HαT, hereditary alpha-tryptasemia; M, male; N, no; N/A, not available; Y, yes.
[a]Confirmed HαT and indolent systemic mastocytosis.

2021

15 y/o female with hives, dyspnea, headache, fatigue
Mast Cell Activation Syndrome

- 3 years of dyspnea, **extreme sensitivity to odors, smells, lotions, tobacco smoke, flushing**, abdominal bloating, pain, throat tightening, fatigue, hives, intolerance to heat, headaches, food and dye intolerance. Fully functional, tennis school team
- PHM: Asthma, Eczema, **SAR on Immunotherapy with anaphylaxis**. Received HPV and restarted IT in 2016 and started reacting to foods, developed hives, dizziness/POTS. Very restricted diet (10 foods)

Tryptase: 3.7 ng/ml

IgE: 38 specific IgE + dust mites, dog

Prostaglandin F2a 14,990 (Nl: < 5000pg/ml Cr)

Classification of Diseases associated with Mast Cell Activation

Akin , Metcalfe, Valent JACI 2010

1. Primary
a. Hypotension with an associated clonal proliferative mast cell disorder (mastocytosis)
b. MMAS*
2. Secondary
a. Allergic disorders
b. Mast cell activation associated with chronic inflammatory or neoplastic disorders
c. Physical urticarias†
d. Chronic autoimmune urticaria
3. Idiopathic‡
a. Anaphylaxis
b. Angioedema
c. Urticaria
d. MCAS§

Non-Clonal Mast Cell Activation Syndrome

Hamilton et al JACI 2011

TABLE II. Signs and symptoms of patients with MCAS

Sign or symptom	Total (%), n = 18
Abdominal pain	17 (94)
Dermatographism	16 (89)
Flushing	16 (89)
Headache	15 (83)
Poor concentration and memory	12 (67)
Diarrhea	12 (67)
Naso-ocular	7 (39)
Asthma	7 (39)
Anaphylaxis	3 (17)

TABLE I. Baseline characteristics of patients with MCAS

Characteristic	No. of patients (%)
Sex	
Male	2 (11)
Female	16 (89)
Age (y)	
20-29	1 (6)
30-39	4 (22)
40-49	8 (44)
50-59	5 (28)
Patients with medication allergy	13 (72)
Patients with food allergy and/or environmental allergy	6 (33)
Endoscopy and abdominal imaging before referral	12 (67)
Mean no. of years symptomatic before referral	4.6
Range of years before referral	1-9

Hamilton et al 2011 JACI

Mast Cell Activation Symptoms and Associated Mediators

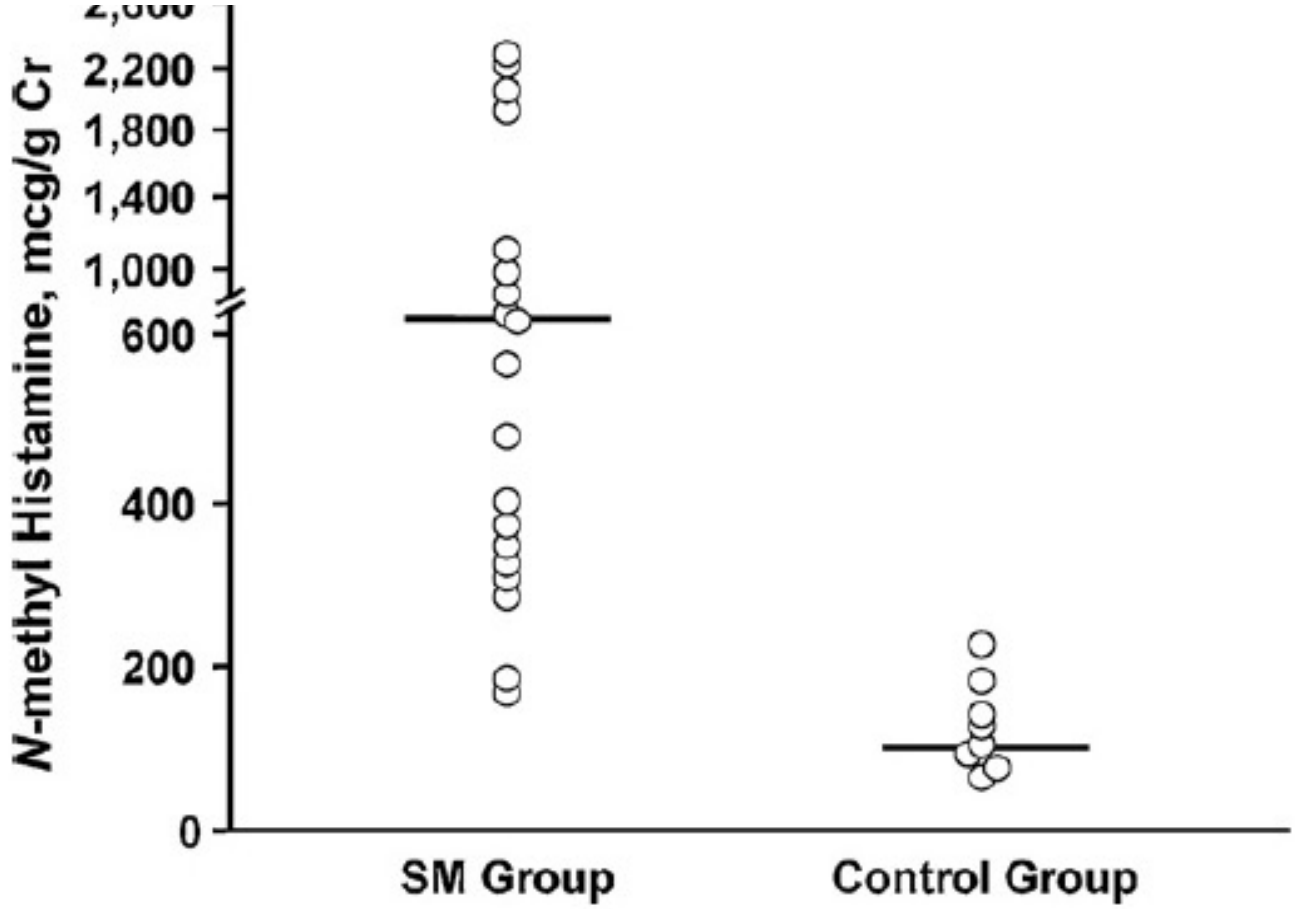
Table 1 Mast cell mediators and related symptoms

	Mediator(s)	Measured in mastocytosis
Systemic		
Vasodilation/hypotension	Histamine	+
	Prostaglandin D2	+
Hypertension	Chymase	–
Fatigue/cachexia/weight loss	TNF-α	+
Fever	IL-6	+
	IL-1	–
Fibrosis	IL-1	–
	IL-13	–
	TGF-β	–
Skin		
Flushing	Histamine	+
	Prostaglandin D2	+
Urticaria/angioedema	Histamine	+
	Prostaglandin D2	+
	Leukotriene C4	–
Gastrointestinal		
Abdominal pain	Histamine	+
Peptic		
Colic		
Diarrhea	Histamine	+
Malabsorption		
Bone		
Bone pain		
Osteoporosis/osteopenia	IL-6	+
	Heparin	–
	Tryptase	+
	TGF-β	–
Central nervous system		
Mixed CNS syndrome	Prostaglandin D2	+
	Histamine	+

Escribano L, Akin C, Castells M, A, Metcalfe DD: Mastocytosis: current concepts in diagnosis and treatment. Annals of Hematology 2002; 81: 677-690

Urinary N-methyl histamine (mcg/g creatinine [Cr]) in systemic mastocytosis and controls

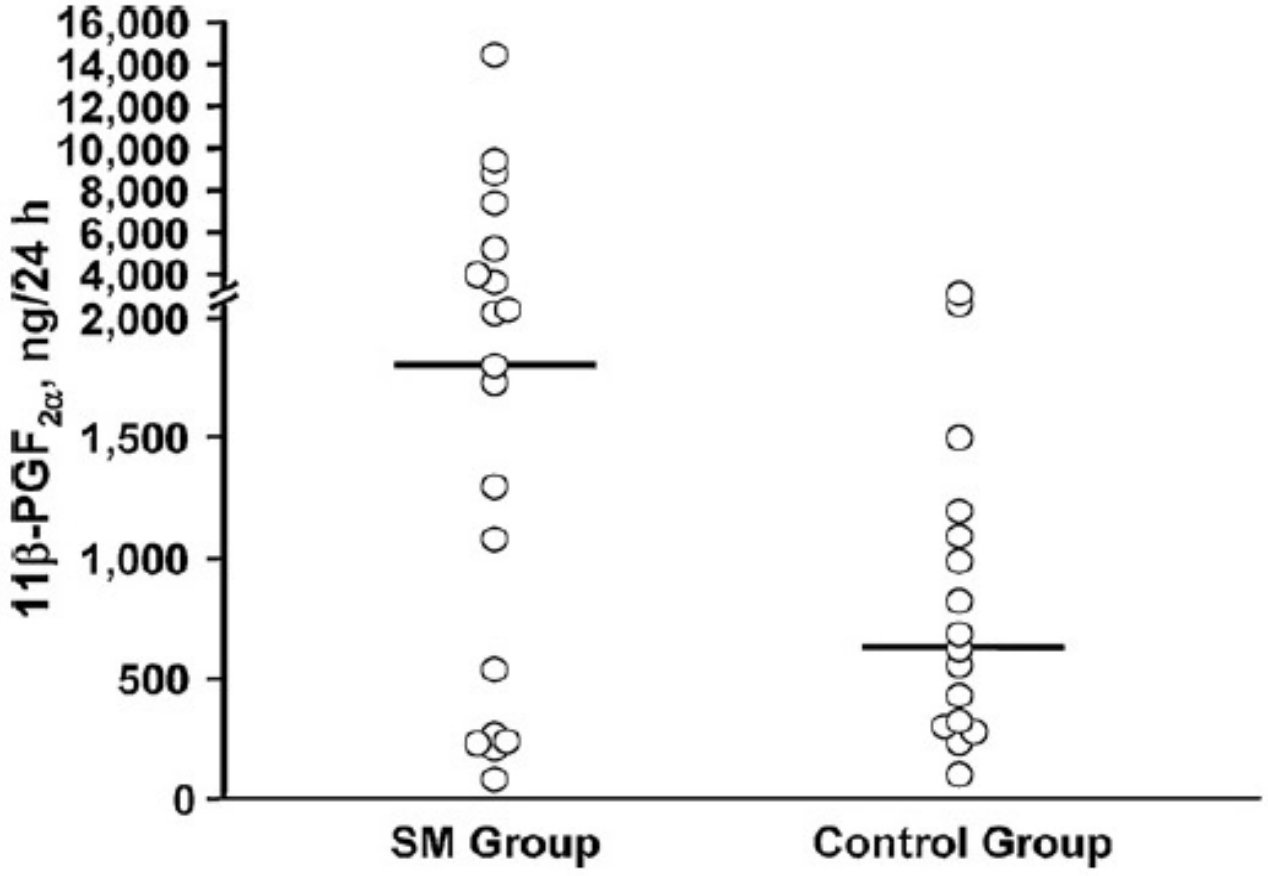
Normal value:
30–200 mcg/g Cr.



Butterfield 2010

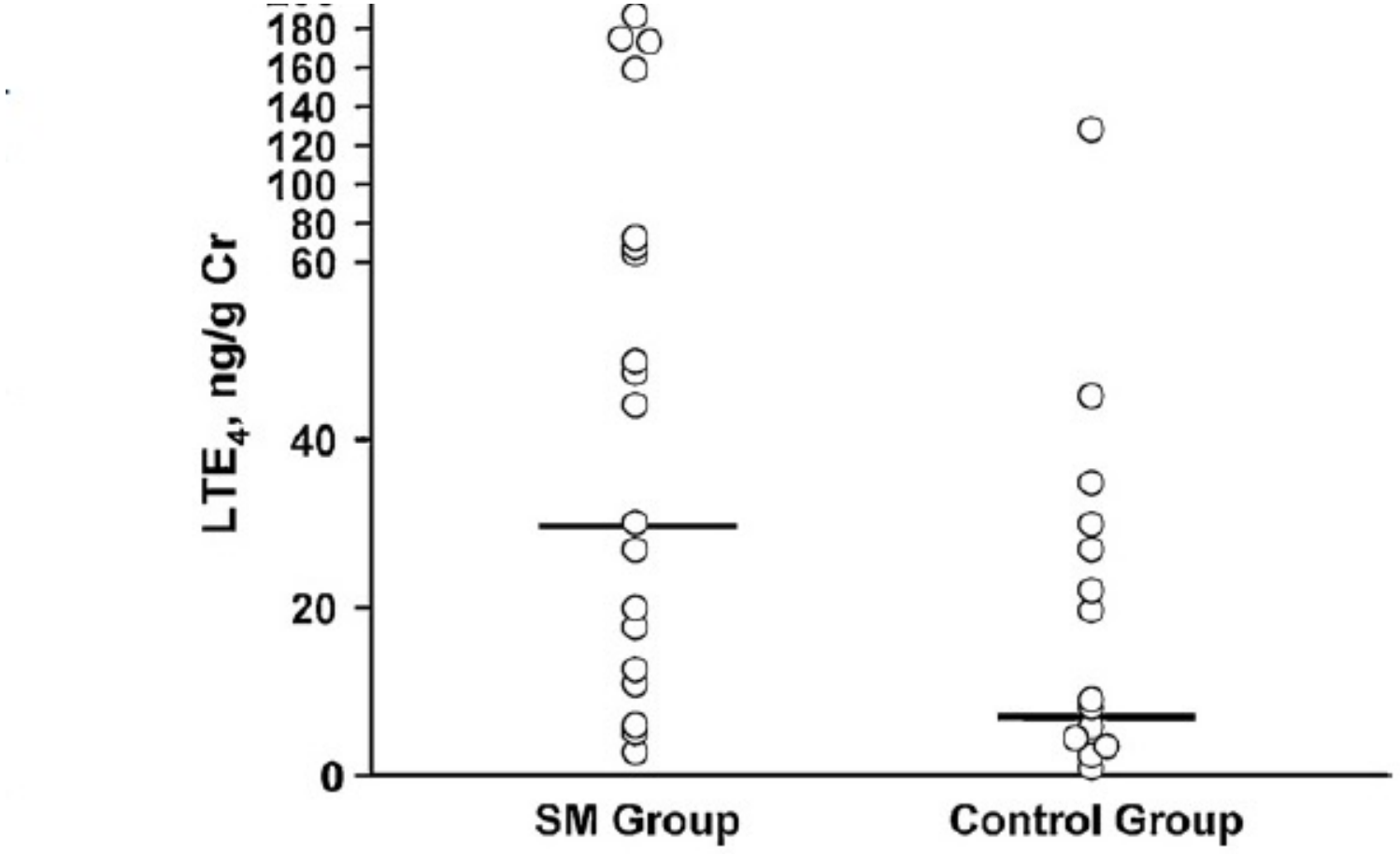
24-h urinary excretion of 11-prostaglandin F2 (11-PGF2) (ng/24 h) in systemic mastocytosis and controls

Normal value:
<1000 ng/24 h



Butterfield 2010

Urinary Excretion of LTE4 (ng/g creatinine) in Patients with Systemic Mastocytosis and Controls

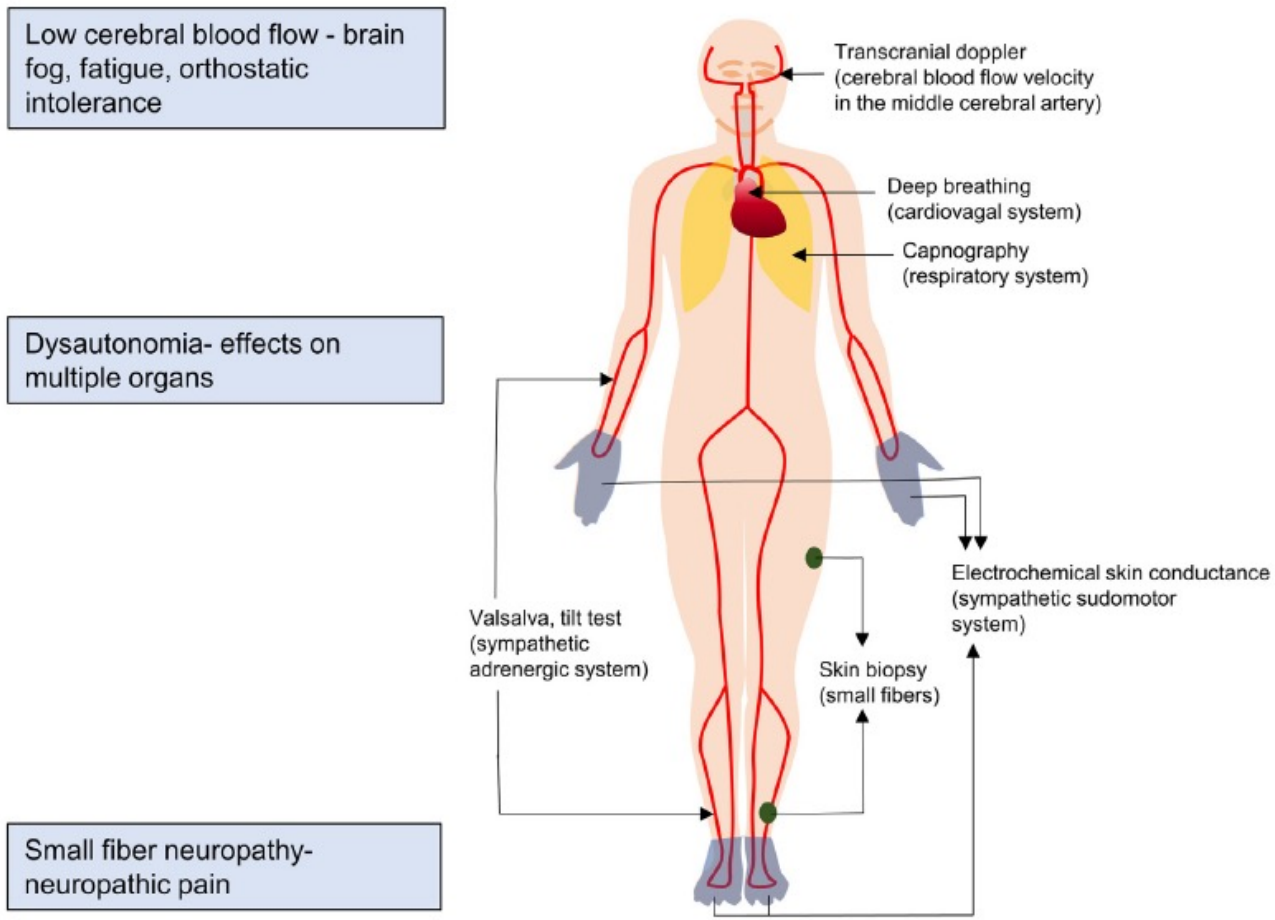


Butterfield 2010

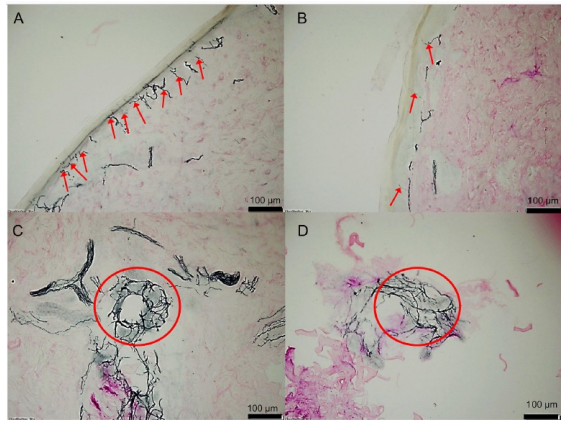
Mast cell disorders are associated with decreased cerebral blood flow and small fiber neuropathy

Peter Novak, MD, PhD[*,†]; Matthew P. Giannetti, MD[†,‡]; Emily Weller, BA[‡]; Matthew J. Hamilton, MD[†,§]; Mariana Castells, MD, PhD[†,‡]

[*] *Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts*
[†] *Harvard Medical School, Boston, Massachusetts*
[‡] *Division of Allergy and Clinical Immunology, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts*
[§] *Division of Gastroenterology, Endoscopy, and Hepatology, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts*



igure 1. The Brigham protocol for comprehensive autonomic testing. The cartoon reveals the specific tests performed and the targeted physiological systems.



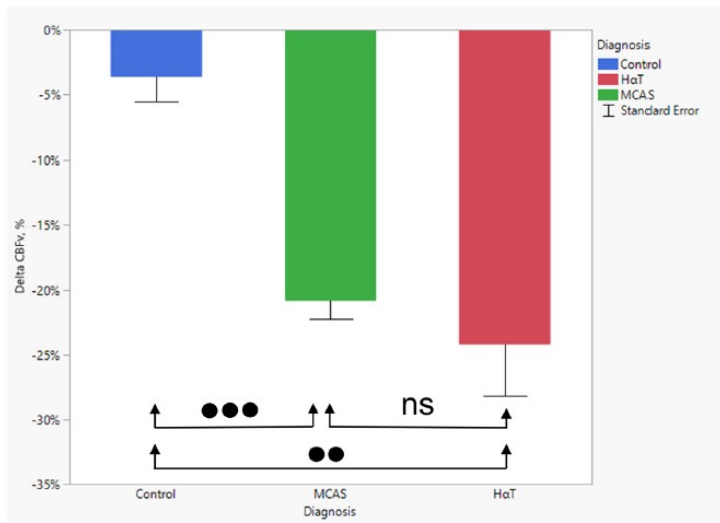


Figure 3. CBFv at the tenth minute of the tilt in the patients with HαT and MCAS compared with controls (••:P <.001; •••: P <.001; ns, not significant). HαT, hereditary alpha tryptasemia; MCAS, idiopathic mast cell activation syndrome

TABLE II. Approach to mast cell mediator–induced symptoms in mastocytosis and MCAS.

A. Avoidance of triggers: patient specific
Specific foods, medications (NSAIDs, vancomycin, quinolones), environmental allergens, and general triggers (stress, lack of sleep, emotions)
Physical triggers (exercise, rubbing, pressure)
Changes in temperature (heat, cold)
Extreme temperatures
Dryness of skin
B. Premedications recommended for surgery, invasive procedures (endoscopy, colonoscopy, others), radiological procedures with contrast dyes, dental procedures, and vaccinations: 12 and 1 h
• Antihistamine receptors H1 and H2
• Leukotriene blocker
• Steroid (0.5-1 mg/kg)
C. Management of cutaneous mastocytosis:
Local care of skin
Skin moisturizer
Water-soluble sodium cromolyn cream/ointment (1% to 4%)
Avoid friction, pressure, and temperature changes
Consider surgical excision for mastocytomas (flexures, soles, palms, scalp)
Steroid creams
PUVA (psoralens)

Personalized Medicine
Targeting Mediators and Symptoms

Mast Cell Activation Syndrome and Mastocytosis: Initial Treatment Options and Long-Term Management

JACI In Practice 2019

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TABLE III. Targeted approach for mast cell mediators–related symptoms in mastocytosis and MCAS

Systems and symptoms	Medications targeting mast cell mediators
Skin: pruritus, flushing, urticaria, angioedema, dermatographism	
1	H1-blockers and H2-blockers:
	Cetirizine 10 mg up to QID
	Loratadine 10 mg up to QID
	Fexofenadine 180 mg up to QID
	Hydroxyzine 10-25 mg QID
	Cyproheptadine 4 mg TID
	Doxepin 10-50 mg
	Ranitidine 150-300 mg BID
	Cimetidine 300 mg BID
	Pepcid 20-40 mg dq
2	Leukotriene receptor blockers/ antagonist
	Montelukast 10 mg
	Zileuton 650 mg BID
3	Aspirin 81-650 mg BID
4	Ketotifen 1-2 mg BID
5	4% sodium cromolyn cream/ ointment
Gastrointestinal: diarrhea, abdominal bloating, cramping/ pain, nausea, vomiting, GER	
1	H2-blockers (as per above)
2	Cromolyn sodium 100-200 mg QID
3	Proton pump inhibitors (as per above)
4	Leukotriene receptor blockers/ antagonists (as per above)
5	Ketotifen 1-2 mg BID

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Neuro/psychiatric: headache, poor concentration, short memory span, brain fog, anxiety, depression		
1		H1-blockers and H2-blockers (as per above)
2		Cromolyn sodium (as per above)
3		Ketotifen (as per above)
		Aspirin (as per above)
Cardiovascular: presyncope, syncope, tachycardia, hypotension, hypertension		
1		H1-blockers and H2-blockers
2		Corticosteroids 0.5-1 mg/kg
3		Epinephrine 0.3-0.5 mg
Pulmonary: wheezing, shortness of breath, throat swelling		
1		Bronchodilators
		Steroid/bronchodilator combination
2		H1-blockers and H2-blockers (as per above)
3		Corticosteroids 0.5-1 mg/kg
4		

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Anaphylaxis	
Acute	Epinephrine IM 0.3-0.5 mg
	Corticosteroids (0.5-1 mg/kg) X1 dose
	IV fluids
	Antihistamine receptors H1 and H2
Prevention	H1-blockers and H2-blockers
	Leukotriene blockers
	Corticosteroids 0.5-1 mg/kg
	Omalizumab 300 mg every 28 days
Hymenoptera-induced	Venom immunotherapy
	Omalizumab 300 mg every 28 days
Naso-ocular: nasal stuffiness, nasal pruritus, conjunctival injection	H1-blockers (as per above)
	Inhaled corticosteroids
	Nasal cromolyn sodium
Bone: osteopenia, osteoporosis, bone fractures	Calcium, Vit D
	Biphosphonates
	Clodronate, pamidornate, alendronate, zolendronate
	Interferon alpha 2a

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Oral Disodium Cromoglycate in the Treatment of Systemic Mastocytosis

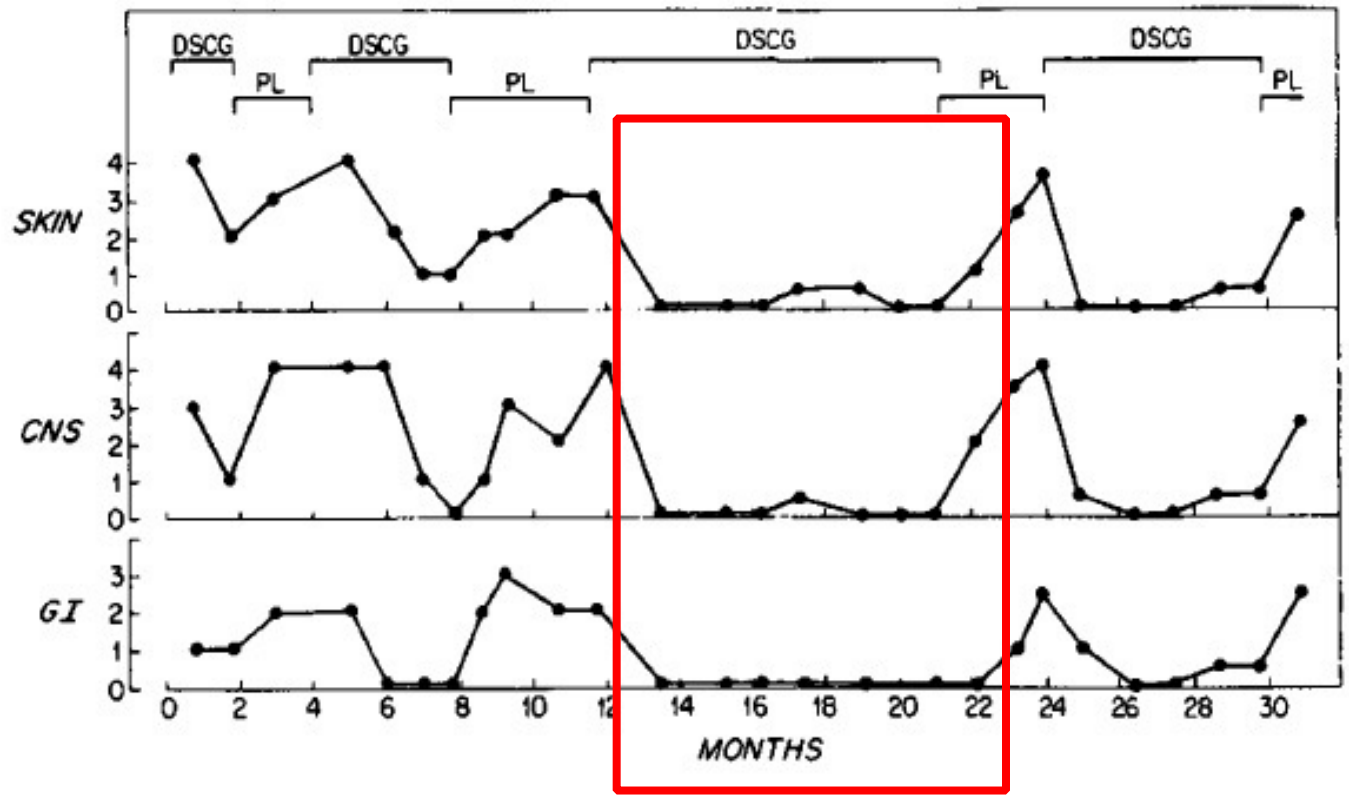
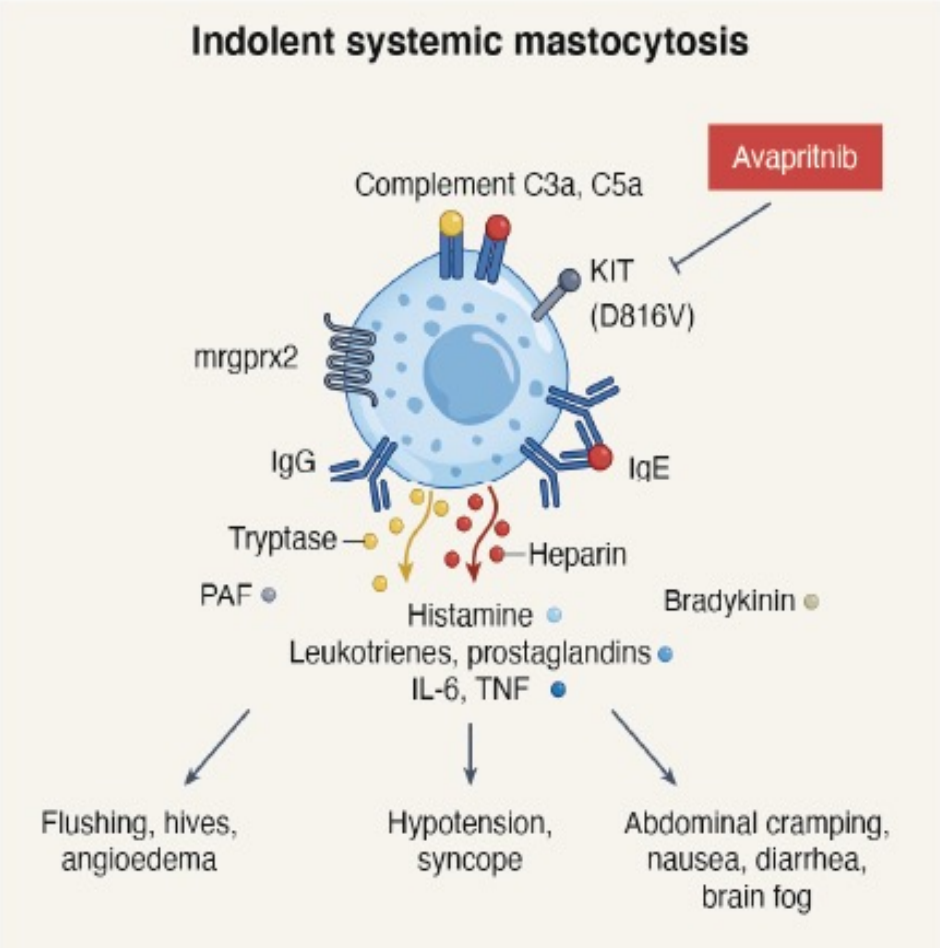
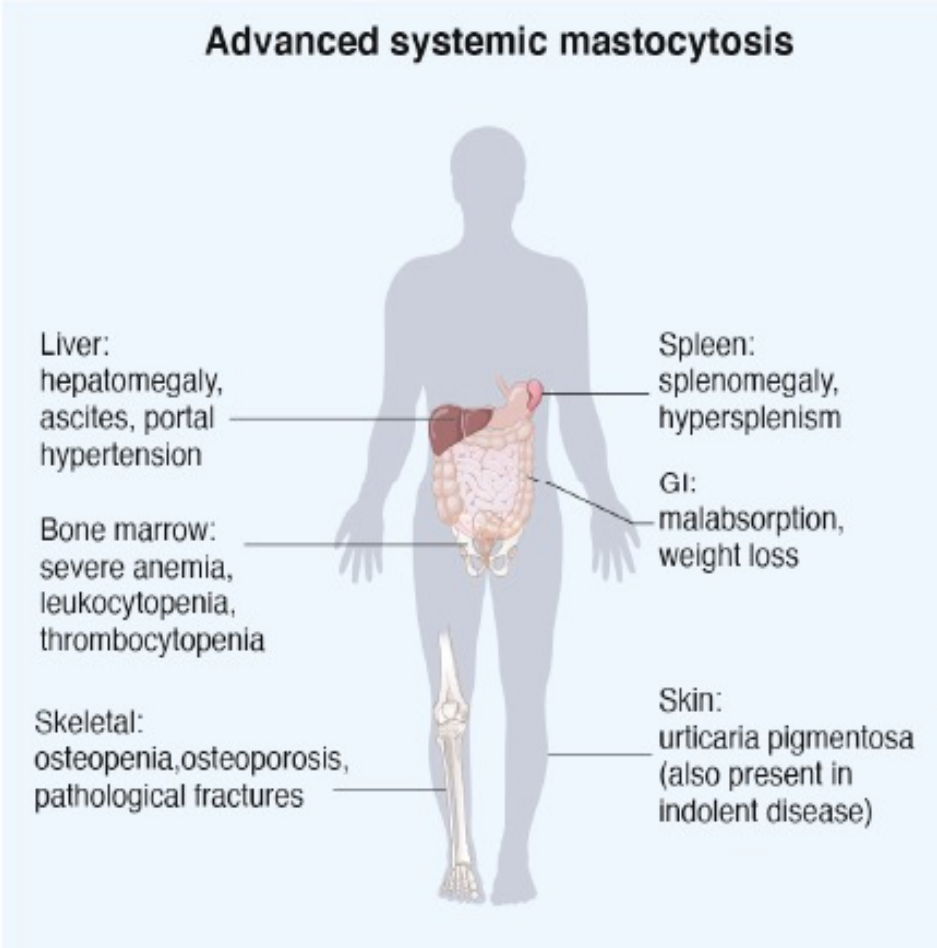


Figure 1. Time Course of Effect of Disodium Cromoglycate and Placebo in Patient 1.

Soter NA, Austen KF, Wasserman SI: Oral disodium cromoglycate in the treatment of systemic mastocytosis. New England Journal of Medicine 1979; 301: 465-469

New Treatment Options for Mastocytosis and Mast Cell Activation Symptoms



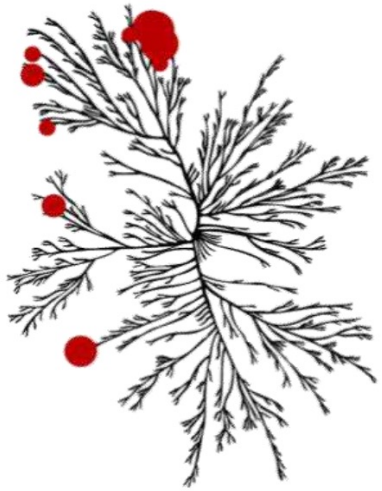


Castells, M; Akin, C. Nature Medicine 2022

First Targeted Therapy Approved for Rare Mutation of Gastrointestinal Stromal Tumors

Avapritinib: a highly selective and potent KIT/PDGFRA inhibitor for GIST

GIST mutation(s)		Medical need by mutation	Avapritinib biochemical IC_{50}[1]
KIT Exon 11 deletion	JM domain	1L imatinib is effective 2L sunitinib/3L regorafenib have low ORR/short PFS	0.6 nM
KIT Exon 11 V560G			1 nM
KIT Exon 11/13	ATP binding site	Approved 2L/3L agents have low ORR/short PFS	11 nM
KIT Exon 11/14			28 nM
KIT Exon 11/17	Activation loop		0.1 nM
PDGFRα D842V		No highly effective therapy in any line	0.24 nM



Avapritinib kinome selectivity

Ongoing clinical trials

NAVIGATOR GIST

Phase 1 advanced GIST

VOYAGER GIST

Phase 3 trial of avapritinib vs. regorafenib in 3L and 4L GIST

Severe side effects

Thrombocytopenia

Brain Hemorrhage

KIT, KIT proto-oncogene receptor tyrosine kinase; PDGFRA, platelet-derived growth factor alpha; IC_{50}, concentration causing 50% inhibition; L, line; JM, juxtamembrane; ORR, objective response rate; PFS, progression-free survival.

Kinome illustrations reproduced courtesy of Cell Signaling Technology, Inc. (CSTI) (www.cellsignal.com). Blueprint Medicines is not responsible for the content of the CSTI site.

[1]Evans E, et al. Sci Transl Med. 2017;9(414). pii: eaao1690.

Jan2020

Mastocytosis and Mast Cell Activation Syndromes Treatment

- **Phenotypes: MCAS, HaT , Mastocytosis**
- **Comorbidities: anaphylaxis, allergies, POTS, EDS, SFN**
- **Diagnosis: KIT mutations, single cell RNA**
- **New Biomarkers: nanoparticles, signal transduction, receptors MRGPRX2**
- **New Therapies : TKI, ITIMs receptors**

Recent Publications

1. Giannetti MP, Weller E, Alvarez-Twose I, Torrado I, Bonadonna P, Zanotti R, Dwyer DF, Foer D, Akin C, Hartmann K, Rama TA, Sperr WR, Valent P, Teodosio C, Orfao A, Castells M. **COVID-19 infection in patients with mast cell disorders including mastocytosis does not impact mast cell activation symptoms**. J Allergy Clin Immunol Pract. 2021 Feb 23:S2213-2198(21)00203-8. doi: 10.1016/j.jaip.2021.02.023
2. Hamilton MJ, Zhao M, Giannetti MP, Weller E, Hufdhi R, Novak P, Mendoza-Alvarez LB, Hornick J, Lyons JJ, Glover SC, Castells MC, Pozdnyakova O. **Distinct Small Intestine Mast Cell Histologic Changes in Patients With Hereditary Alpha-tryptasemia and Mast Cell Activation Syndrome**. Am J Surg Pathol. 2021 Jan 20. doi: 10.1097/PAS.0000000000001676.
3. Giannetti MP, Weller E, Bormans C, Novak P, Hamilton MJ, Castells M. **Hereditary alpha-tryptasemia in 101 patients with mast cell activation-related symptomatology including anaphylaxis.** Ann Allergy Asthma Immunol. 2021 Jan 17:S1081-1206(21)00024-7. doi: 10.1016/j.anai.2021.01.016.
4. Giannetti MP, Akin C, Hufdhi R, Hamilton MJ, Weller E, van Anrooij B, Lyons JJ, Hornick JL, Pinkus G, Castells M, Pozdnyakova O. **Patients with mast cell activation symptoms and elevated baseline serum tryptase level have unique bone marrow morphology**. J Allergy Clin Immunol. 2020 Nov 25:S0091-6749(20)31633-X. doi: 10.1016/j.jaci.2020.11.017.
5. Rama TA, Moreira A, Castells M. **mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis**. J Allergy Clin Immunol. 2021 Mar;147(3):877-878. doi: 10.1016/j.jaci.2021.01.004
6. *Novak P, Giannetti MP, Weller E, Hamilton MJ, Castells M. **Symptomatic Hereditary Alpha Tryptasemia and Idiopathic Mast Cell Activation Syndrome 2 Patients Present with Decreased Cerebral Blood Flow, Small Fiber Neuropathy, and Autonomic Dysfunction** Annals Oct 2021

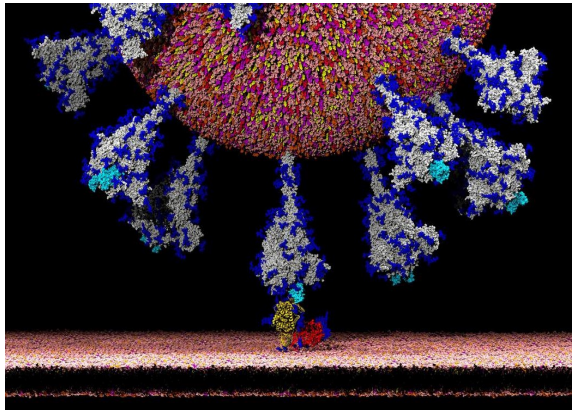
American Initiative in Mast Cell Diseases

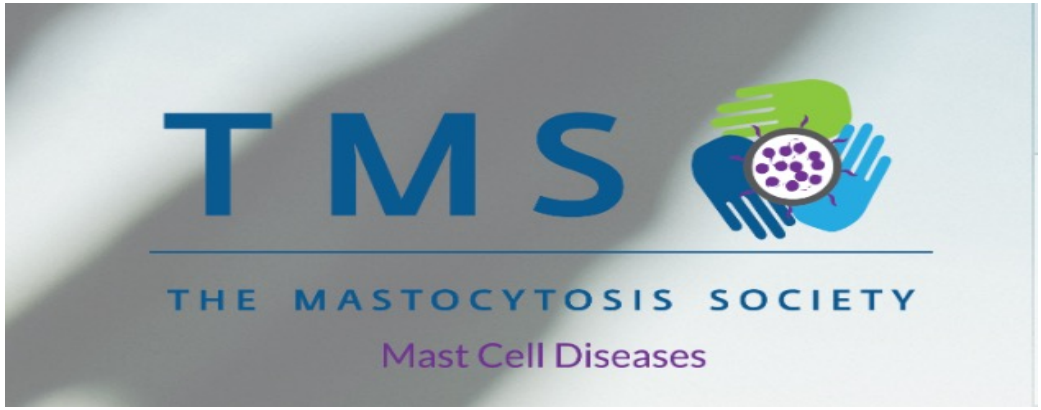
The American Initiative in Mast Cell Diseases (AIM) is a network which will consist of Centers of Excellence and Reference Centers in the United States, Canada, Mexico, Central, and South America. This network will collaborate with the European Competence Network on Mastocytosis (ECNM), which has centers established throughout Europe.

American Initiative in Mast Cell Diseases

2021 VIRTUAL MEETING ● SALT LAKE CITY, UT

April 1, 2021



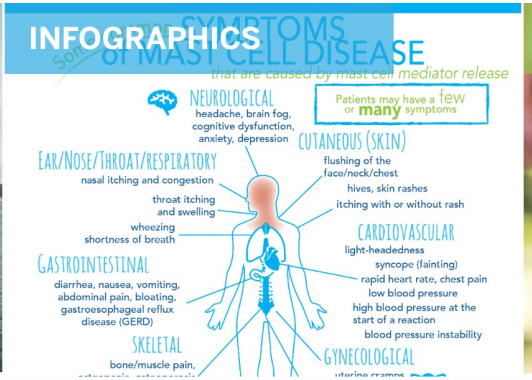


The Mastocytosis Society

is a non-profit organization dedicated to supporting patients affected by Mastocytosis and Mast Cell Activation Diseases as well as their families, caregivers and physicians through research, education and advocacy.

LEARN MORE >

THE MASTOCYTOSIS SOCIETY



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