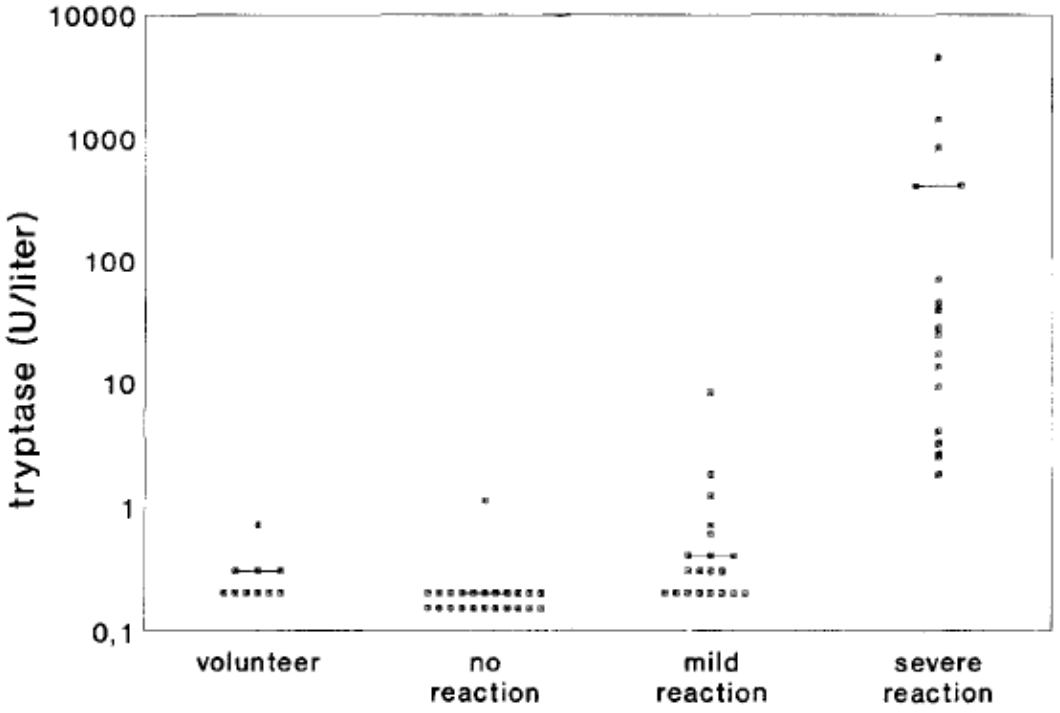
A familial cause of mast cell activation and connective tissue abnormalities

Joshua Milner MD
Genetics and Pathogenesis of Allergy Section
Laboratory of Allergic Diseases

National Institute of
Allergy and
Infectious Diseases

What is tryptase?



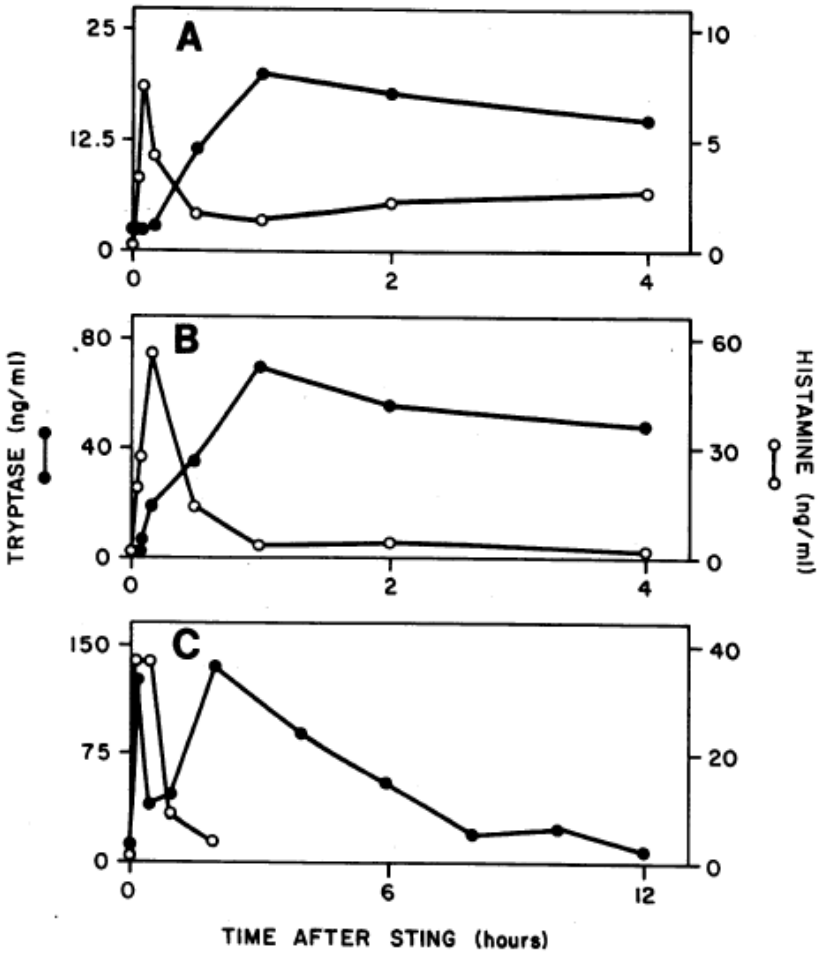
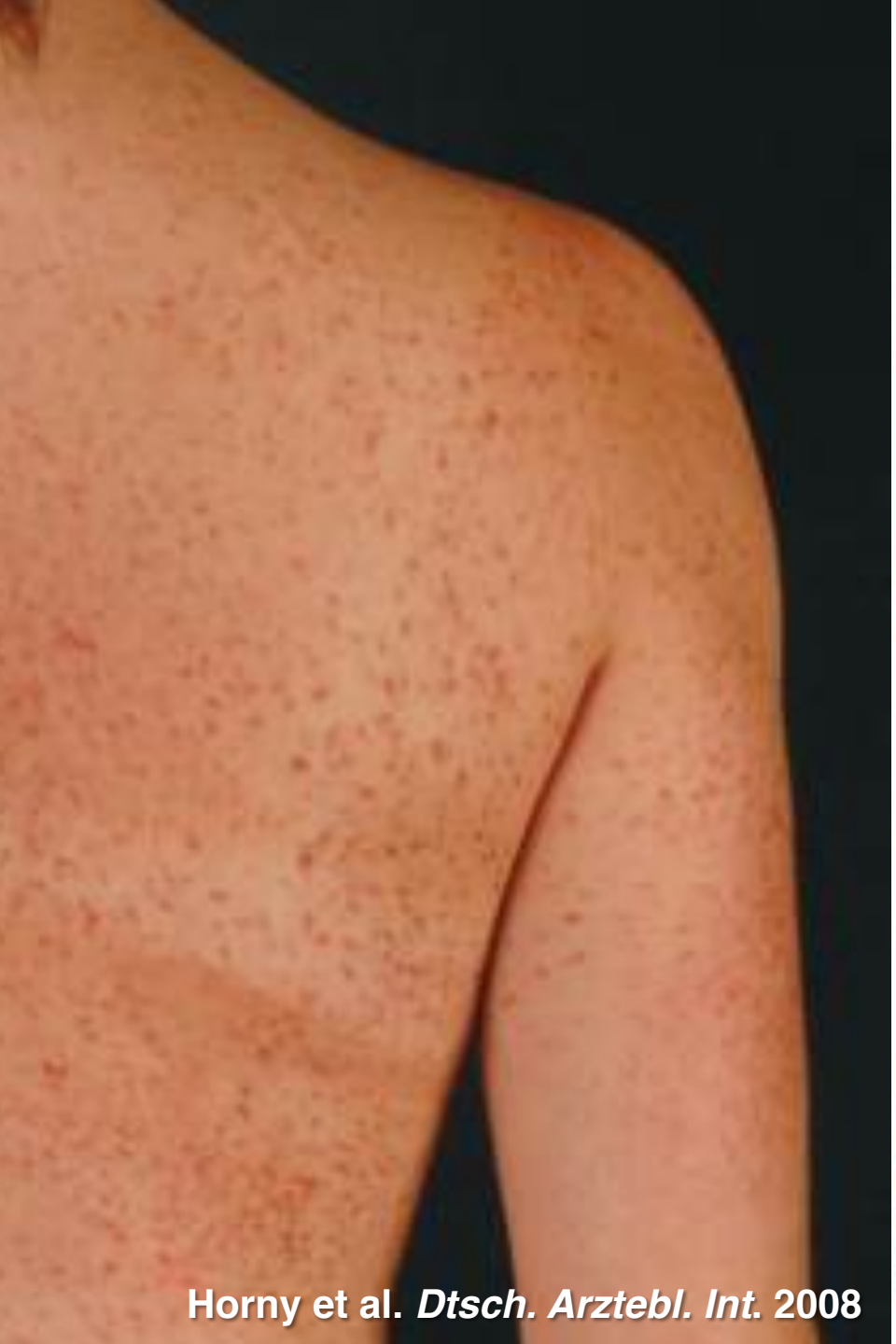


Figure 1. Plasma tryptase (●) and histamine (○) levels after a bee sting challenge.

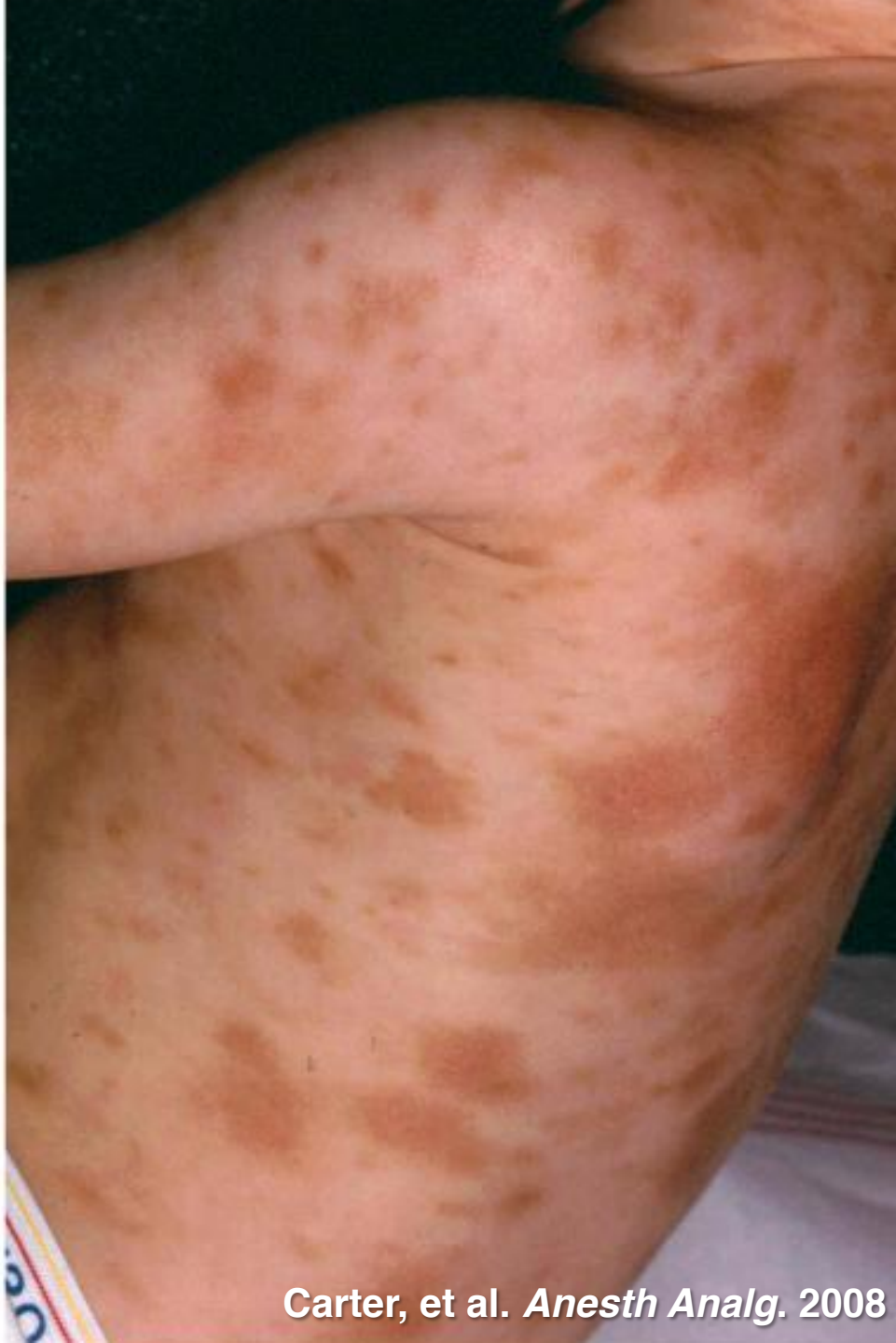
Schwartz et al. *J. Clin. Invest.* 1989
van der Linden et al. *J. Allergy Clin. Immunol*. 1992

Tryptase Clinical Utility: Anaphylaxis & Mast Cell Associated Diseases

- Mature tryptase increased in IgE-mediated reactions
  - systemic
  - not seen with food-induced anaphylaxis
- Mastocytosis: rare clonal proliferative disease
  - Somatic mutations
    - KIT (D816V)
    - FIP1L1-PDGFRα
  - Rare germline forms
    - Diffuse cutaneous mastocytosis
- Mast cell activation syndromes (MCAS)
  - Tryptase may not be elevated
  - No reports to suggest inheritance
    - Similar symptoms reported among family members
  - Clinical diagnosis



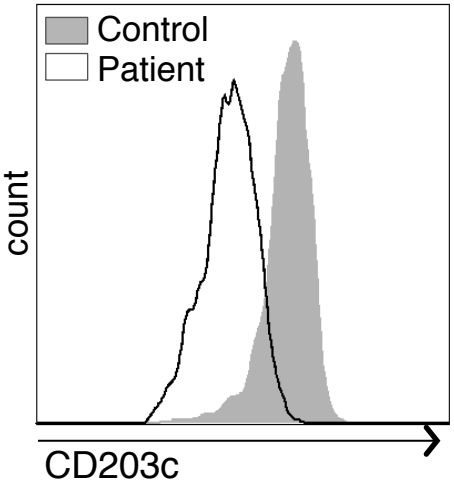
Horny et al. *Dtsch. Arztebl. Int*. 2008

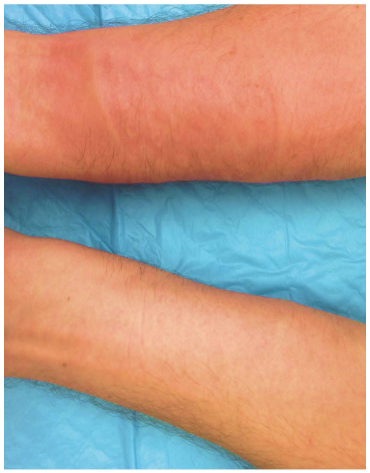


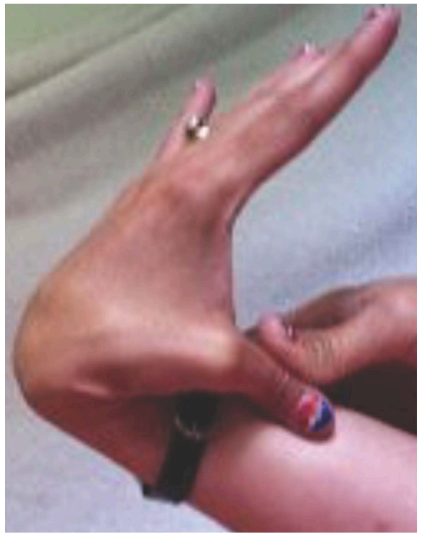
Carter, et al. *Anesth Analg*. 2008

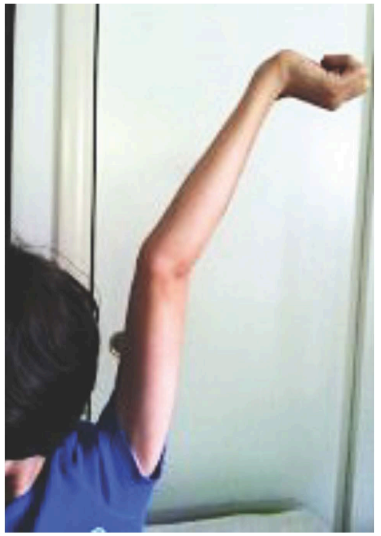
AD familial tryptasemia

- **Hyporesponsive basophils**
- **Cutaneous**
  - Recurrent flushing, pruritus, angioedema, urticaria
- **Connective Tissue**
  - Hypermobile, retained dentition, malformation *eg. pectus/scoliosis*
- **Atopy**
  - Anaphylaxis, AD, Asthma, FA, DA, Rhinitis/Conjunctivitis
- **Gastrointestinal**
  - Episodic pain, urgency, IBS, GERD, EoE, FTT
- **Neuropsychiatric**
  - Dysautonomia, Anxiety/ Depression, Pain, Behavior DO









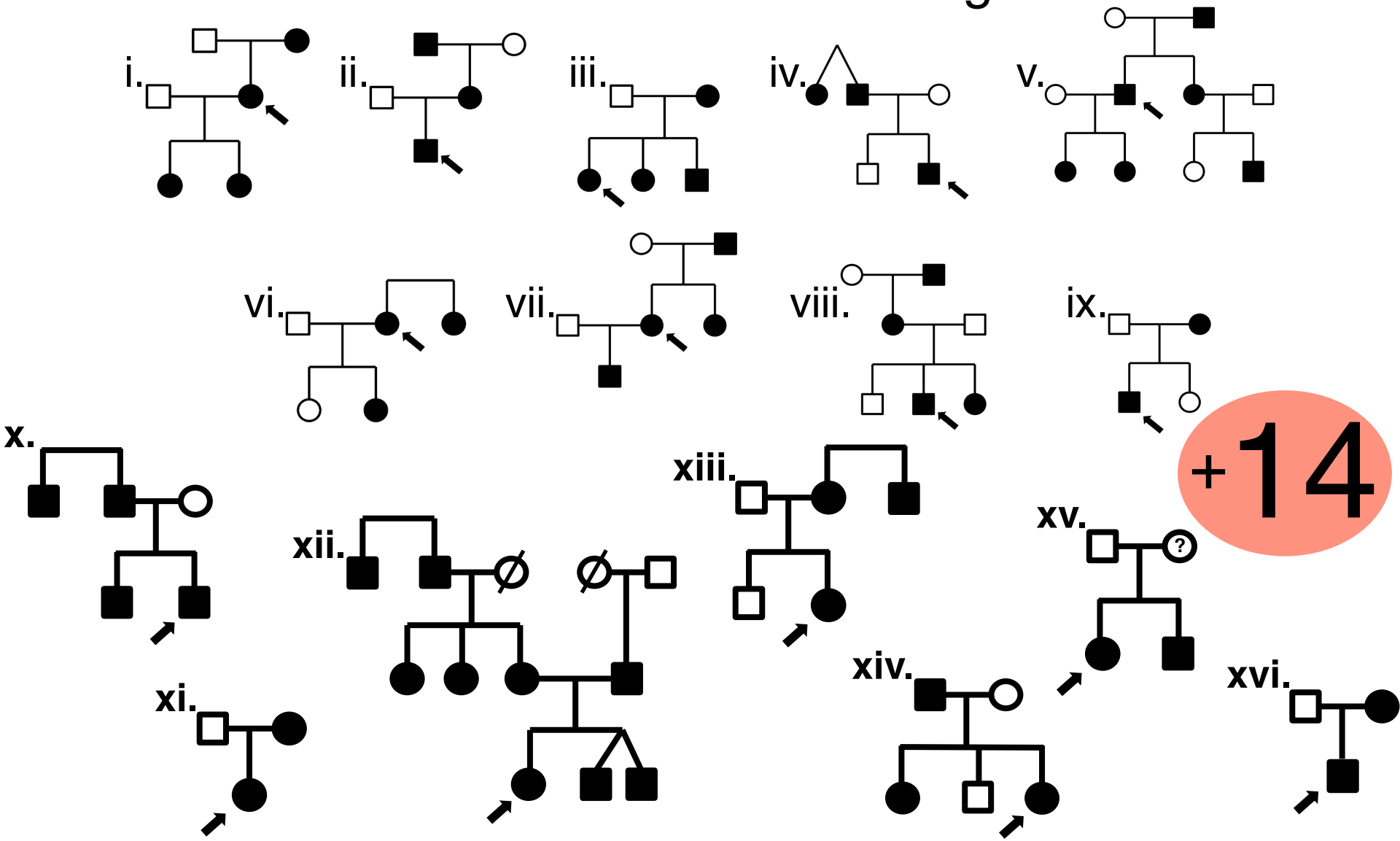
Lyons et al. *J. Allergy Clin. Immunol*. 2014

Additional Symptoms

- Increased cholecystectomy rate
- Increased libido
- Increased bleeding in the absence of any abnormal labs. Gynecologic bleeding in particular

AD familial tryptasemia:

30 families and counting



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

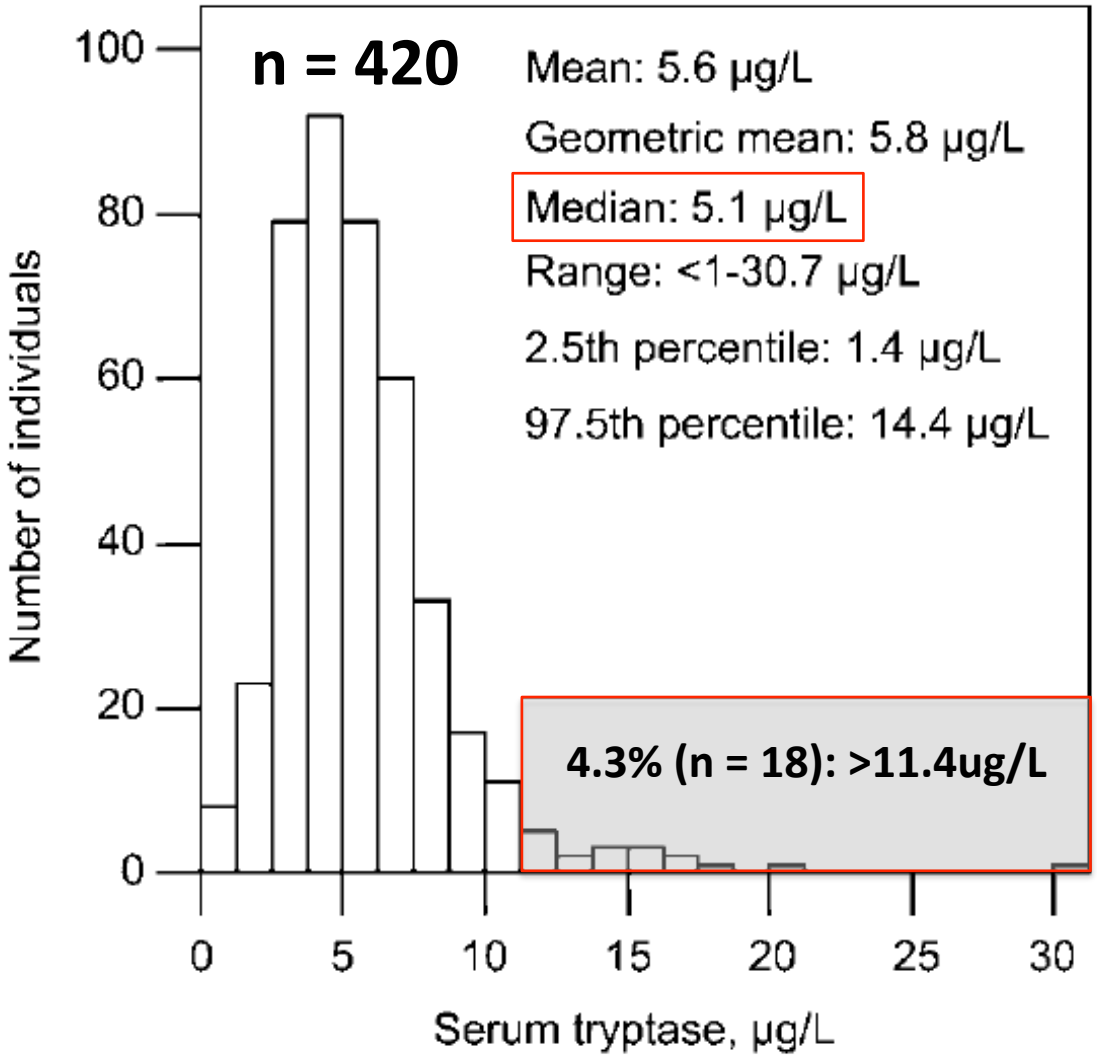
Clinical phenotype segregates with elevated serum tryptase

Table I. Association of clinical characteristics with elevated serum tryptase.

Manifestation	Elevated Tryptase	Normal Tryptase	P-value
Cutaneous	38/49	8/20	<0.005
Connective Tissue	29/49	4/20	<0.005
Atopy	44/49	13/20	<0.05
Gastrointestinal	42/49	7/20	<0.0001
Neuropsychiatric	37/49	5/20	<0.0005

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

Prevalence of tryptasemia in general population



Gonzalez-Quintela. *Clin Chem Lab Med.* 2010

Table 2 Symptoms of 100 patients with elevated basal serum tryptase (BST) and 100 controls. Patients were additionally divided into two groups (slightly elevated BST 11.4–20.0 ng/ml and BST > 20 ng/ml).

	Patients			Controls		
	BST ≥ 11.4 ng/ml	BST 11.4–20.0 ng/ml	BST >20.0 ng/ml	BST ≥ 11.4 ng/ml	χ^2-Test patients vs. controls	Frequency rate[a]
Number (male/female)	100(32/68)	81(26/55)	19(6/13)	0		
Frequency of symptoms						
Fatigue	56%	56%	58%	37%	<0.01	1.5
Meteorism[b]	42%	41%	47%	15%	<0.0001	2.8
Headache	37%	37%	32%	38%	n.s.	1.0
Muscle and bone ache	36%	36%	42%	16%	<0.001	2.3
Swinging mood	36%	32%	47%	19%	<0.01	1.9
Vertigo	31%	30%	37%	8%	<0.0001	3.9
Tachycardia	29%	28%	32%	10%	<0.001	2.9
Flush	25%	25%	26%	7%	<0.001	3.6
Acid reflux	24%	25%	21%	15%	n.s.	1.6
Palpitations	23%	22%	26%	8%	<0.01	2.9
Pruritus	22%	22%	21%	18%	n.s.	1.2
Diarrhoea[b]	22%	20%	32%	8%	<0.01	2.7
Hypotension	18%	16%	26%	7%	<0.05	2.6
Abdominal pain[b]	18%	16%	26%	7%	<0.01	2.5
Angio-oedema	15%	15%	16%	2%	<0.01	7.3
Nausea	14%	14%	16%	4%	<0.05	3.5
Urticaria	10%	9%	16%	4%	n.s.	2.6
Collapse	9%	9%	11%	0%	<0.01	–
Ulcer	6%	7%	0%	0%	<0.05	–
Rash	5%	5%	5%	3%	n.s.	1.7
Vomiting	4%	4%	5%	1%	n.s.	4.0

[a] The frequency rate refers to how much more frequently a certain symptom occurs in patients compared to controls.
[b] Patients with fructose malabsorption and/or lactose intolerance were excluded. Fellinger et al. *Allergol Immunopathol.* 2014

What's causing this?

- Genetic, but there is clearly heterogeneity– many families do not have elevations in tryptase, although within families tryptases remain high in affected patients
- Linkage analysis suggests every family followed so far links to a single locus

Management

- Stepwise, system by system
- H1&H2 blockade, mast cell stabilization, IgE blockade, antiinflammatories
- Trial and error (mostly error)
- Address neuropsychiatric component, but it is neither all physiologic nor all supratentorial.

Acknowledgements & Thanks

NIH, NIAID, LAD
Jon Lyons
Chi Ma
Xiaomin Yu
Guangping Sun
Kendal Karpe
Michael O'Connell
Celeste Nelson
Nina Jones
Tom DiMaggio

NIH, NIA
Clair Francomano
Nazli McDonnell

NIH, NIDDK
Theo Heller
Nancy Ho

NIMH
Maryland Pao

Royal Manchester Children's Hospital
Peter Arkwright

Cincinnati Children's Hospital
Marc Rothenberg
J. Pablo Abonia
Andrew Lindsley

Virginia Commonwealth University
Lawrence Schwartz

Support
NIAID DIR
Merck