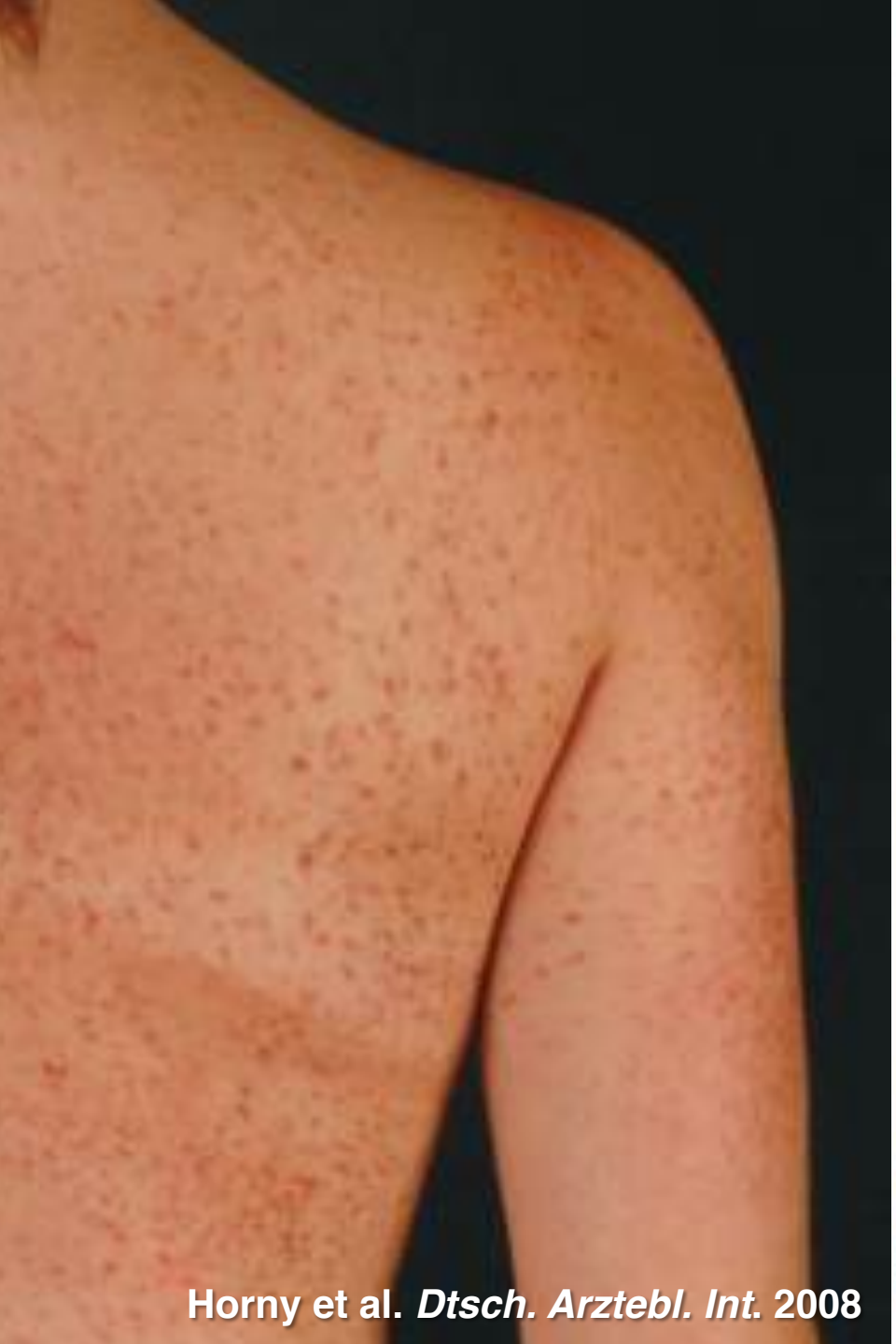
A familial connection between mast cell disorders, EDS and dysautonomia

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

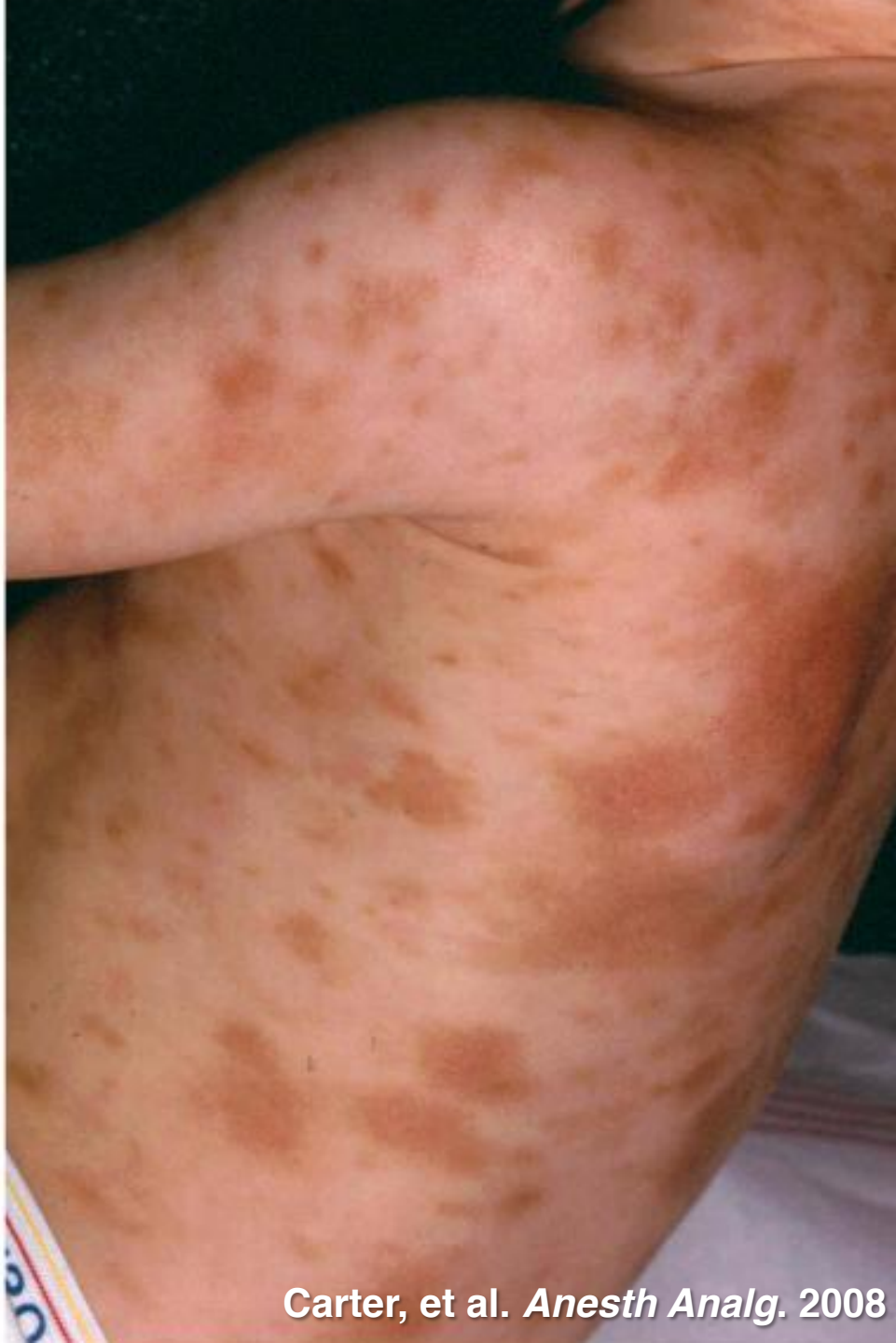
National Institute of
Allergy and
Infectious Diseases

What is serum Tryptase?

- A mast cell content that we can measure when mast cells become activated
- When is it high typically?
  - After an allergic reaction (anaphylaxis)– only temporarily
  - Mastocytosis- having too many mast cells
  - Mast cell activation syndromes (MCAS)



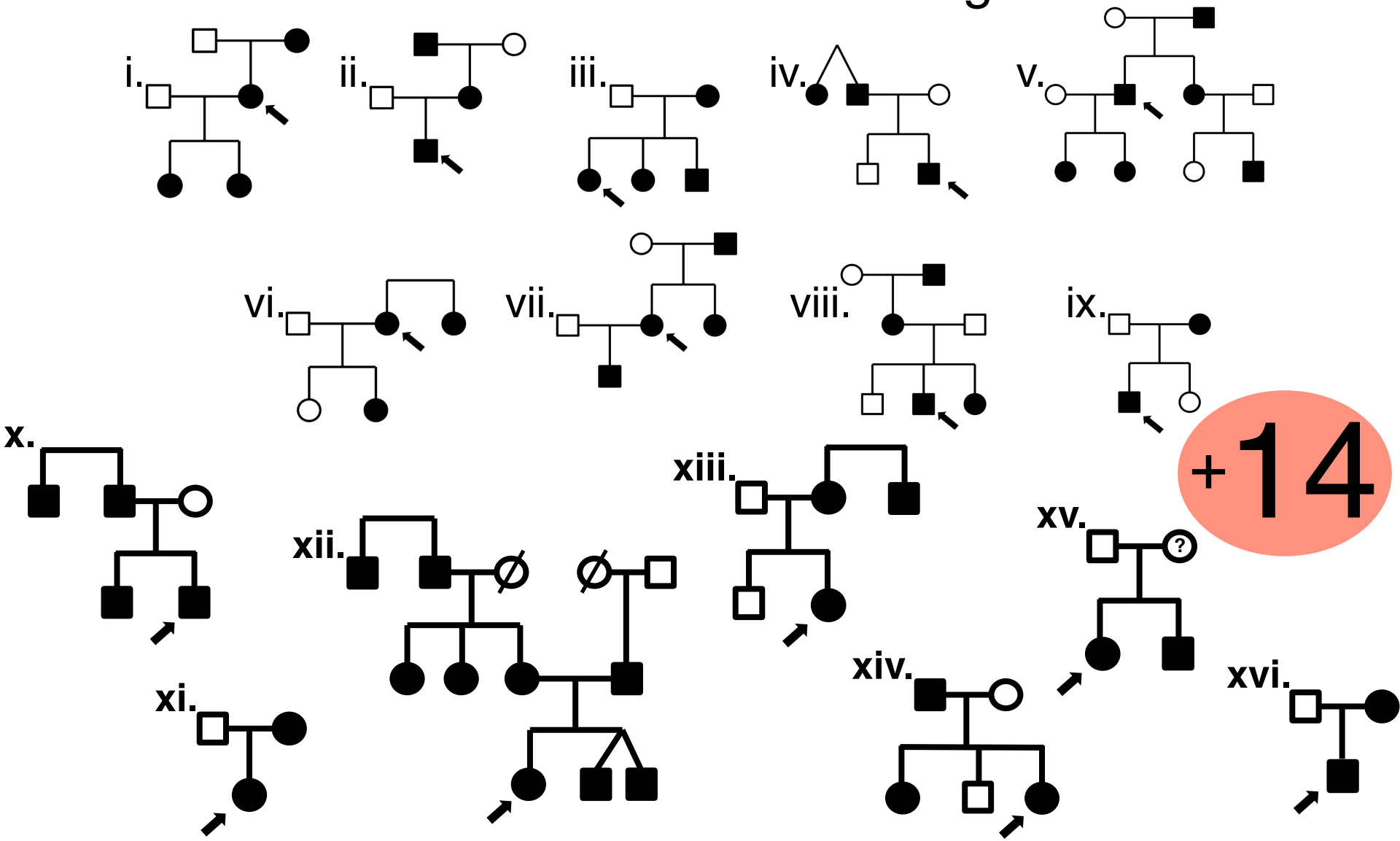
Horny et al. *Dtsch. Arztebl. Int*. 2008



Carter, et al. *Anesth Analg*. 2008

AD familial tryptasemia:

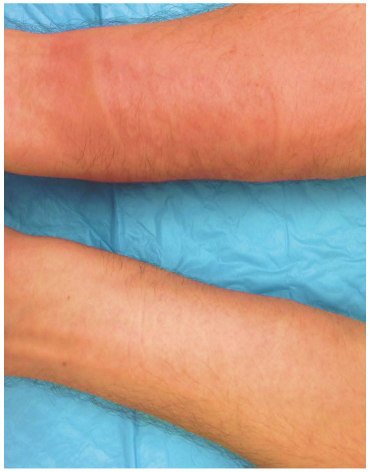
30 families and counting

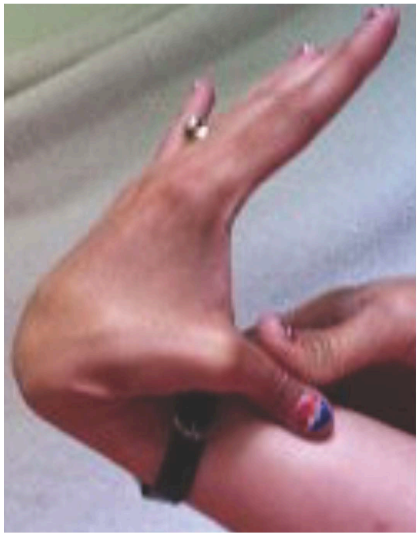


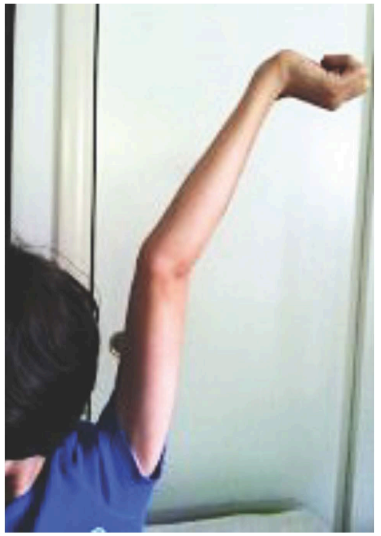
Lyons et al. *J. Allergy Clin. Immunol*. 2014

Familial hypertryptasemia

- **Skin**
  - Recurrent flushing, itching, swelling, hives
- **Connective Tissue**
  - Joint laxity, retained childhood teeth, scoliosis, etc.
- **Allergy**
  - Anaphylaxis, Bee sting allergy, nonallergic food, drug and smell reactions
- **Gastrointestinal**
  - Episodic pain, fecal urgency, IBS, reflux, dysmotility, gallbladder issues
- **Neuropsychiatric**
  - Dysautonomia, Anxiety/ Depression, Pain, Behavior issues

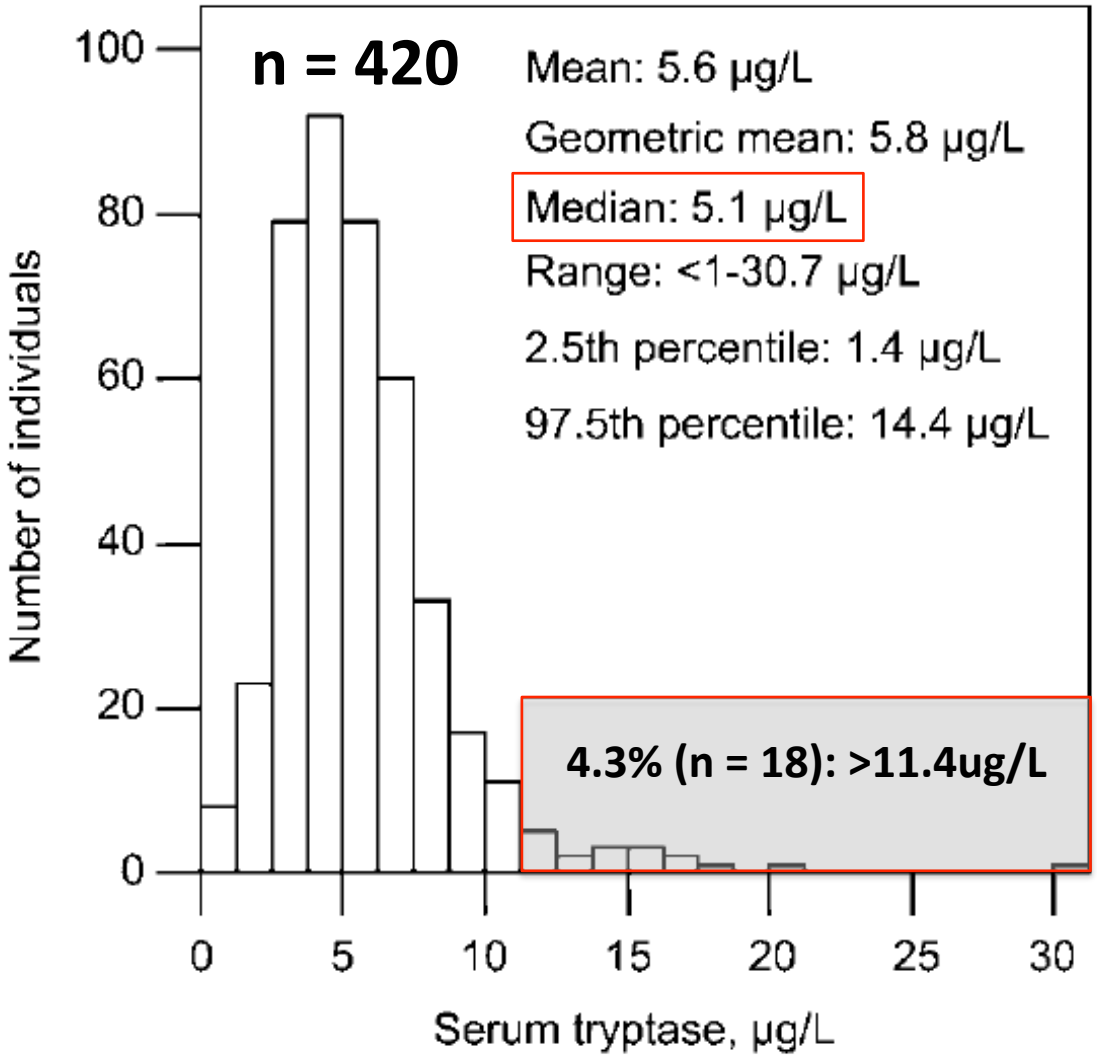






Lyons et al. *J. Allergy Clin. Immunol*. 2014

Prevalence of high tryptase in the 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

How do we treat these families?

- Very similar to mast cell activation syndrome patients
  - Antihistamines (e.g. allegra), ranitidine (zantac), cromolyn sodium (gastrocrom), aspirin, omalizumab (xolair), steroids
  - Biofeedback
  - Consult with GI, genetics, cardiology (for dysautonomia)

Concluding points

- A specific syndrome of high tryptase, symptoms of mast cell activation, EDS-like symptoms and dysautonomia can run in families in a dominant fashion.
- Many of these symptoms can be seen in families who do not have elevated serum tryptase
- Our ongoing research is to find the single genetic cause of this, in the hopes of identifying a target to treat.
- In the meantime, management is symptomatic, not magic!

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