ICD10 Coding Presentation

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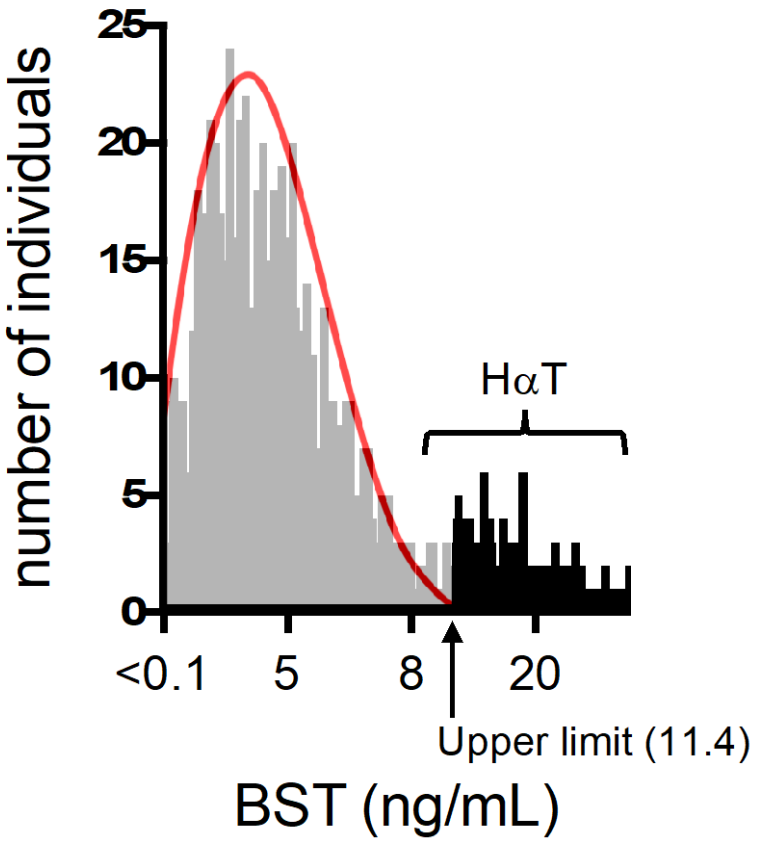
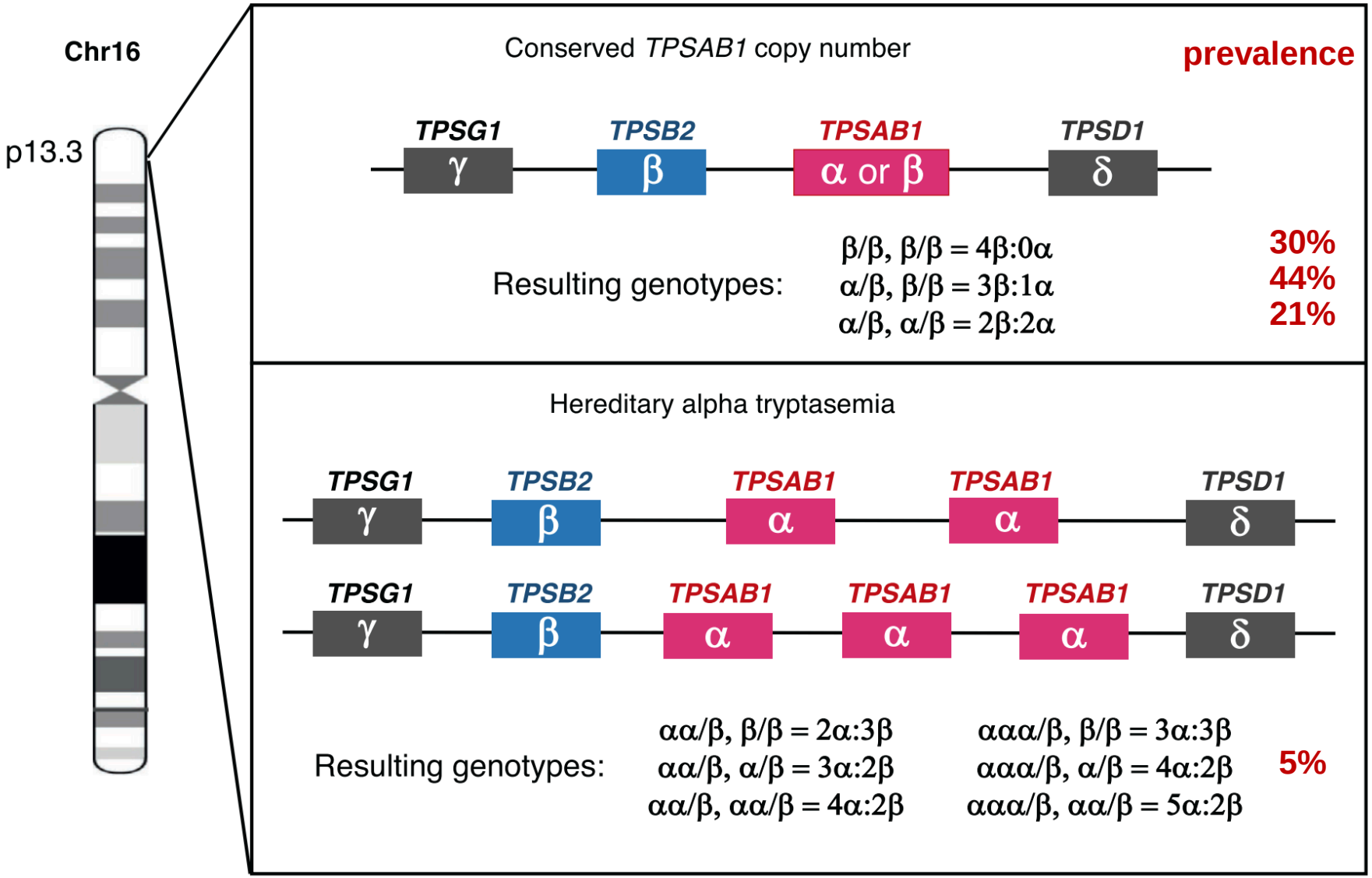
Hereditary α-tryptasemia (HαT): the common cause of elevated serum tryptase

- The upper limit of normal for serum tryptase is 11.4 ng/ml
- Tryptase levels of greater than this have classically been associated with mast cell diseases, myeloproliferative diseases, and anaphylaxis
- Hereditary α-tryptasemia is associated with tryptase levels greater than 7.5 ng/ml and affects 4 to 6 percent of Western populations.



Lyons et al. *JACI.* 2014
Khoury & Lyons. *Curr Allergy Asthma Rep.* 2019

Increased *TPSAB1* copy number underlies HαT



Normal TPSAB1 copy number is 4. Tryptase level is less than 7.5 ng/ml.

A duplication in TPSAB1 copy number means there is one extra copy. Tryptase is greater than 7.5 ng/ml and can be has high as 30 ng/ml.

Lyons et al. *Nat Genet.* 2016
Lyons. IAC. 2018

Multisystem complaints associated with HαT

Table 1
Clinical features reported in association with hereditary alpha tryptasemia

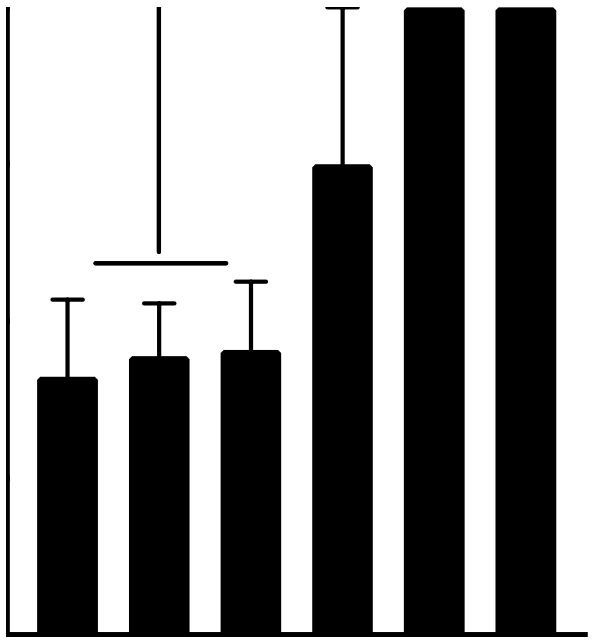
Manifestation	Reported Prevalence,[a] %	Association Supported in an Unselected Cohort[b]
Basal serum tryptase >8 ng/mL	100	Yes
Chronic gastroesophageal reflux symptoms	56–77	No
Arthralgia	44–45	No
Body pain/headache	33–47	No
Flushing/pruritus	32–55	Yes
Irritable bowel syndrome (Rome III)	28–49	Yes
Sleep disruption	22–39	No
Systemic immediate hypersensitivity reaction	21–28	No
Retained primary dentition	20–33	Yes
Systemic venom reaction	14–22	Yes
Congenital skeletal abnormality	11–26	No
Joint hypermobility	0–28	No
Positive Tilt-table test	0–11	No

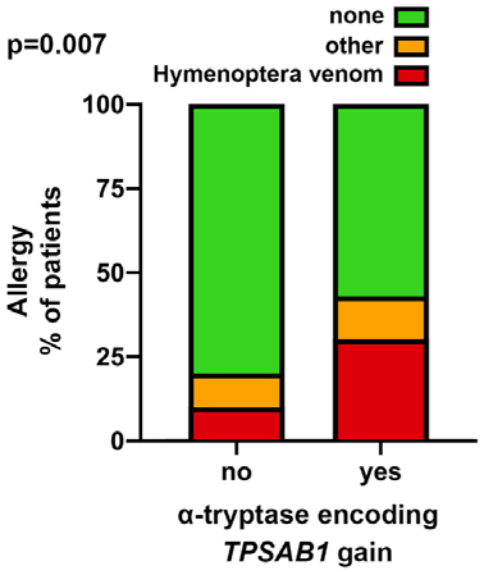
[a] In order of reported prevalence, ranges are derived from available data in 3 reports.[14,15,17]
[b] Finding was identified as significantly associated with increased *TPSAB1* copy number in an unselected volunteer adult population.

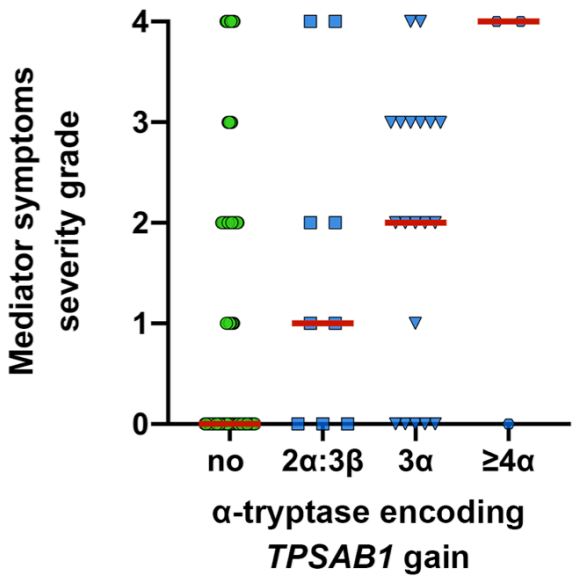
- GERD
- Joint pian
- Body pain/headache
- Flushing and itching
- Abdominal pain
- Sleep disruption
- Systemic immediate hypersensitivity reaction
- Retained primary dentition
- Systemic venom reaction
- Congenital skeletal abnormality
- Joint hypermobility
- Positive tilt table test

Lyons et al. *Nat Genet.* 2016
Lyons. IAC. 2018

HαT is a *bona fide* modifier of clonal mast cell disease



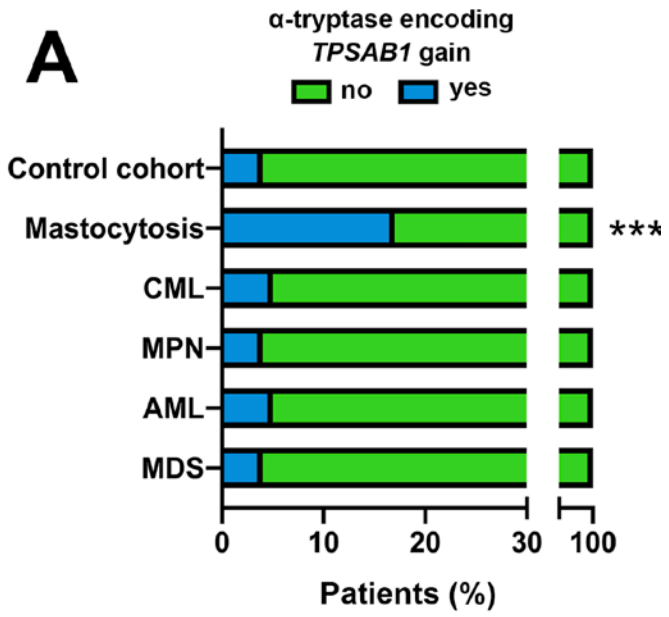


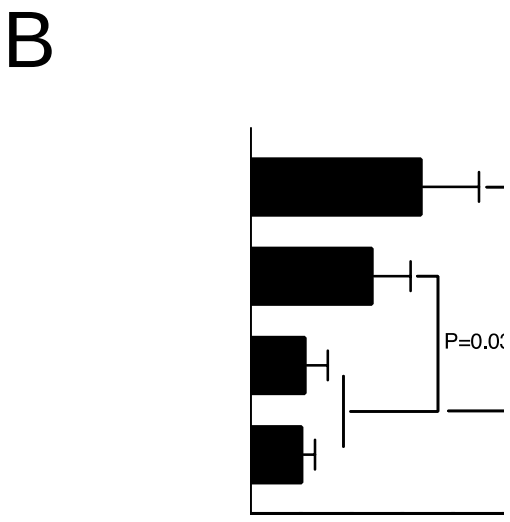


- Systemic anaphylaxis is associated with tryptase copy number more than 5. This is statistically significant.
- It is also associated with increased reaction to bee venom and mast cell mediator symptoms.

Lyons et al. *JACI* 2020
Greiner et al. *Blood* 2020

HαT prevalence is increased in clonal and non-clonal mast cell disease

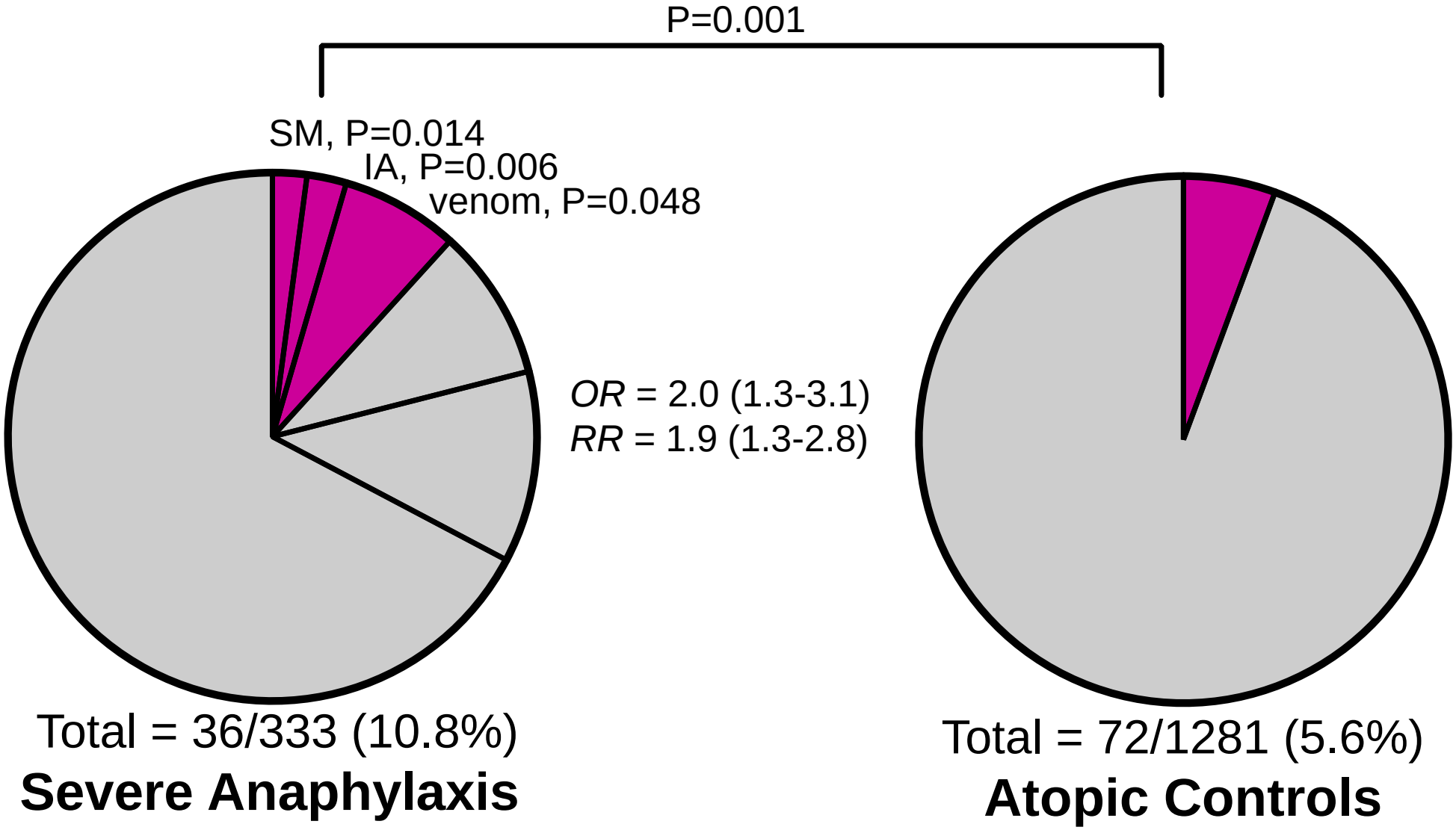




- HαT prevalence is increased in patients with mastocytosis, CML, MPN, AML, MDS
- It is also increased in idiopathic anaphylaxis and systemic mastocytosis.

Lyons et al. *JACI* 2020
Greiner et al. *Blood* 2020

HαT is the first identified heritable risk for severe anaphylaxis



Lyons et al. *JACI* 2017
Lyons et al. *JACI* 2020

Conclusions

- Increased α-tryptase encoding *TPSAB1* copy number is the cause of hereditary α tryptasemia (HαT)
- HαT is a genetic trait affecting 4-6% of Western populations and is the common cause for basal serum tryptase elevations
- Individuals with IA and ISM are significantly more likely to have HαT
- HαT modifies symptoms of mast cell mediator release, including anaphylaxis, as well as disease related symptoms and severity
- Increased *TPSAB1* copy is associated with increased risk for severe anaphylaxis (in the context of HVA, IA, ISM)
- The diagnosis of HαT is currently used in HVA and ISM in order to risk stratify patients and identify those at high risk of severe anapylaxis