Hereditary Alpha-Tryptasemia May Act as a Disease Modifier in Inflammatory Bowel Disease

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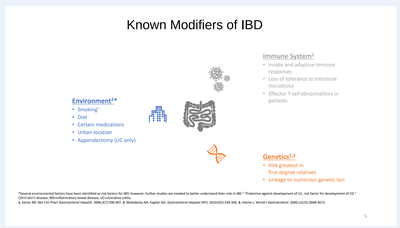
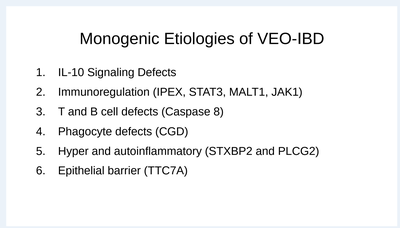
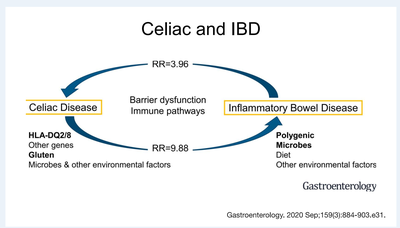
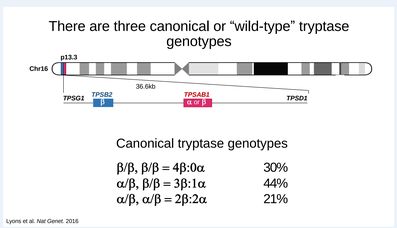
Introduction

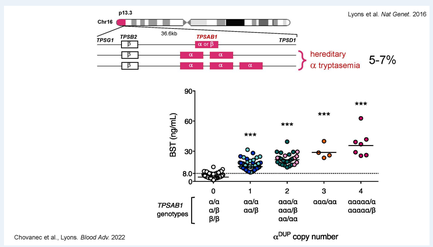
Hereditary alpha-tryptasemia (HαT, ICD-10 D89.44) is an autosomal dominant genetic trait present in up to 6% of individuals of European ancestry. Approximately, 1/3 of individuals with this genetic trait are symptomatic.
Typically, individuals with symptomatic HαT present with skin, nerve, or GI manifestations and a tryptase of >8 ng/ml. HαT is independently associated with an increased risk of anaphylaxis. Diagnosis is confirmed by performing digital droplet PCR to confirm extra copies of alpha-tryptase encoding *TPSAB1* (>2) which is located on chromosome 16. Major GI symptoms include esophageal reflux, abdominal pain, diarrhea, constipation, and gastrointestinal food sensitives. We have previously shown that HαT is associated with increased mast cell numbers, accelerated epithelial pyroptosis (inflammatory cell death), and increased class switched memory B cells in the small intestine in absence of a gut inflammatory disorder.

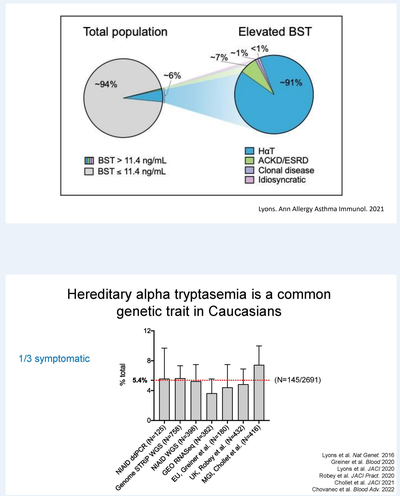












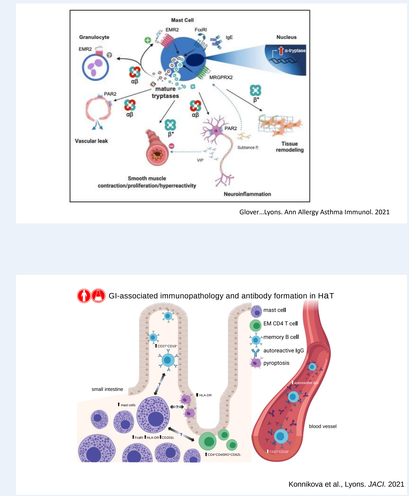


Table 1. Demographics and Clinical Characteristics of HαT/IBD Patients (N=8)

Patients	Age	Gender	Race/Ethnicity	Copies of Alpha Tryptase Gene	Copies of Beta Tryptase Gene	Total TPSAB1 Copies	Tryptase Level
1*	53	Female	Caucasian	2	2	4 (beta loss)	18
2	47	Male	Caucasian	3	2	5	17.5
3	32	Female	Caucasian	3	2	5	10.6
4	52	Male	Caucasian	4	2	6	34.5
5	51	Female	Caucasian	3	2	5	13
6	41	Male	Caucasian	2	3	5	12
7	51	Female	Caucasian	2	3	5	16
8	40	Male	Caucasian	2	3	5	17

*Patient that has beta loss. Glover SC, Carlyle A, and Lyons JJ. Hereditary alpha-tryptasemia despite normal tryptase-encoding gene copy number owing to copy number loss in trans. *Ann Allergy Asthma Immunol* 2022;128(4):460-461.

Table 3. Current IBD Therapy and Failed Therapy for HαT/IBD Patients (N=8)

Patients	Current IBD Therapy	Additional Current IBD Therapy (If Multiple)	Failed Medications
1	Upadacitinib	N/A	N/A
2	Ustekinumab	IMM	Steroids, Infliximab, Adalimumab
3	Steroids	Tofacitinib	Steroids, IMM, 5-ASA, Infliximab, Adalimumab, Ustekinumab
4	Tofacitinib	N/A	Steroids, IMM
5	IMM	Adalimumab	Steroids, 5-ASA
6	Upadacitinib	Tofacitinib	Steroids
7	Tofacitinib	Steroids	Adalimumab, IMM, Ustekinumab, Infliximab, Vedolizumab
8	Upadacitinib	N/A	Steroids, Infliximab, 5-ASA, IMM

Abbreviations: IMM, Immunomodulators; 5-ASA, 5-Aminosalicylates

Table 2. Disease Phenotype and Surgical History of HαT/IBD Patients (N=8)

Patients	Disease Type	Age at Diagnosis (Years)	CD Phenotype	CD Location	UC Extent	Surgical History
1	CD	51	Inflammatory	Colonic	N/A	None
2	CD	40	Penetrating	Colonic	N/A	Colectomy
3	CD	3 months	Penetrating	Ileocolonic	N/A	None
4	CD	20	Inflammatory	Ileocolonic	N/A	Ileocolic Resection
5	UC	49	N/A	N/A	Left-sided	None
6	CD	36	Inflammatory	Ileal	N/A	Ileocolic Resection
7	CD	9	Inflammatory	Ileocolonic	N/A	None
8	CD	15	Inflammatory	Ileocolonic	N/A	Ileal Resection

Table 4. Summary of HαT/IBD Data

UMMC HαT/IBD Data	N=134	
Percentage of HαT Patients with IBD	5.97%	
Percentage of HαT Patients with Crohn's	5.22%	
Percentage of HαT Patients with UC	0.75%	
Percent of Cohort Diagnosed before 20 yo	50.00%	N=8
Percentage of Cohort on Multiple Medications	62.50%	N=8
Average Number of Failed Medications	3	
Percent of Cohort Failing 3+ Medications	50.00%	N=8
Percent of Patients Requiring Surgery	50.00%	N=8
Average Tryptase Level of Cohort	17.32	N=8
Percent of Cohort with Tryptase 16+	62.50%	N=8

Tables 1- 4. Demographics and clinical history for the patient cohort.

Methods

Our tertiary academic center follows large, well characterized HαT population (n=134). Within this population, we noted that 8 individuals had been diagnosed with either Crohn's or ulcerative colitis. To better understand the impact of HαT on inflammatory bowel disease (IBD), we gathered data on age of IBD diagnosis, number of advanced IBD therapies tried, number of surgeries, average basal serum tryptase (BST) levels, and response to current IBD therapy.

Results

Of the 8 individuals with HαT and IBD, 7 had Crohn's disease and 1 had pan-colonic ulcerative colitis. 50% of the individuals in this cohort were diagnosed prior to age 20. Five of eight patients underwent bowel resection for treatment of Crohn's. On average, the individuals in this cohort had failed at least 3 advanced IBD therapies. The average BST was 17.3 ng/ml. Six of eight patients experienced endoscopic remission on a JAK inhibitor (tofacitinib or upatacitanib). Two of eight patients experienced clinical improvement with ustekinumab.

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Discussion

Our data indicates that IBD appears to be more common and severe in individuals who also have HαT (IBD prevalence in the general population is estimated to be 1.3% but in this symptomatic HαT cohort with GI complaints, it is 6%). Future studies are needed to understand whether or not HαT acts as a disease modifier in IBD.

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