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REPORT

Hereditary alpha-tryptasemia modifies clinical phenotypes among individuals with congenital hypermobility disorders

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Abstract

Hereditary alpha-tryptasemia (HαT) is an autosomal dominant (AD) genetic trait characterized by elevated basal serum tryptase ≥8 ng/mL, caused by increased α-tryptase-encoding *TPSAB1* copy number. HαT affects 5% to 7% of Western populations and has been associated with joint hypermobility. Hypermobility disorders are likewise frequently AD, but genetic etiologies are often elusive. Genotyping of individuals with hypermobility spectrum disorder (n = 132), hypermobile Ehlers-Danlos syndrome (n = 78), or axial skeletal abnormalities with hypermobility (n = 56) was performed. Clinical features of individuals with and without HαT were compared. When analyzing our combined cohorts, dysphagia (p = 0.007) and retained primary dentition (p = 0.0003) were significantly associated with HαT, while positive associations with anaphylaxis (p = 0.07) and pruritus (P = 0.5) did not reach significance likely due to limited sample size. Overall, HαT prevalence is not increased in individuals with hypermobility disorders, rather linked to a unique endotype, demonstrating how HαT may modify clinical presentations of complex patients.

Report

Hereditary alpha-tryptasemia (HαT) is an autosomal dominant genetic trait characterized by elevated basal serum tryptase ≥8 ng/mL. HαT is caused by increased α-tryptase encoding *TPSAB1* copy number on a single allele and is common among Caucasians, affecting 5% to 7% of the Western populations in which this has been studied.[1-5] It has been associated with symptoms suggestive of mast cell-mediator release as well as a number of multisystem complaints, notably certain congenital connective tissue abnormalities including joint hypermobility, scoliosis, retained primary teeth, and less commonly, nail/patella syndrome, ankle protonation, valgus deformity, neonatal clubbing without cardiopulmonary disease, webbed neck, torticollis, club feet, hip dysplasia, pectus excavatum, high arched palate, syndactyly, genus valgus, pes planus, tibial torsion, hyperlordosis, and alveolar mandibular hypoplasia.[1-4,6-9] However, these findings have largely been reported among populations of individuals highly selected for comorbid conditions such as these, leading to potential referral or ascertainment biases.

In addition to studies of symptomatic individuals with HαT, clinical studies have also described an association between symptoms of mast cell activation and connective tissue abnormalities as well.[10,11] While data are limited, it is estimated that two-thirds of individuals with HαT may be asymptomatic.[1,3] However, two recent independent studies have demonstrated HαT to be a major modifier of clonal and non-clonal mast cell-associated disorders, including systemic mastocytosis, idiopathic anaphylaxis, and venom allergy, where individuals with HαT were 2- to 3-fold more likely to present with these disorders and to have severe mast cell-mediator symptoms including anaphylaxis.[2,5] Thus, we set out to determine whether HαT was associated with connective tissue abnormalities in well-characterized cohorts of individuals recruited for connective tissue disorders and/or whether HαT modifies clinical phenotypes or presentations of these individuals, independent of recruitment or ascertainment biases linked to centers specializing in mast cell-associated disorders or syndromic presentations of allergic inflammation.

Tryptase genotyping of *TPSAB1* and *TPSB2* [MIM: 191801] was performed using droplet digital PCR, as described,[3] in two cohorts. The first cohort was composed of individuals with hypermobility spectrum disorder (HSD) and hypermobile Ehlers-Danlos syndrome (hEDS [MIM: 130020]). These individuals were assessed by their respective rheumatologists, allergists, and clinical geneticists to determine diagnoses. The second cohort was composed of individuals with axial skeletal abnormalities, namely with pediatric-onset scoliosis or Chiari malformation, who had concomitant joint hypermobility resulting from hypermobile Ehlers-Danlos syndrome or a Beighton score of ≥6. Approximately half of the second cohort had clinical phenotypes, prompting formal medical

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Table 1. Clinical manifestations associated with HαT among individuals with joint hypermobility disorders

	HSD and hEDS					HSD, hEDS, and axial skeletal abnormality with hypermobility				
	HαT (n = 9)	no HαT (n = 201)				HαT (n = 11)	no HαT (n = 225)			
Manifestation	**n (%)**	**n (%)**	**OR (95% CI)**	**RR (95%CI)**	**p value**	**n (%)**	**n (%)**	**OR**	**RR**	**p value**
Anaphylaxis	1 (11)	5 (3)	4.8 (0.4–32.5)	4.47 (0.7–23.1)	0.2	2 (18)	8 (4)	5.9 (1.1–26.4)	5.0 (1.3–17.1)	0.07
Pruritus	4 (57)	45 (42)	1.8 (0.5–7.4)	1.3 (0.6–2.2)	0.5	5 (56)	51 (39)	1.9 (0.5–6.5)	1.4 (0.7–2.3)	0.5
Inflammatory bowel disease	0 (0)	2 (1)	0 (0.0–49.1)	0 (0.0–36.7)	>0.99	0 (0)	3 (1)	0 (0.0–24.1)	0 (0.0–22.2)	>0.99
IBS-like symptoms	4 (44)	31 (26)	2.2 (0.7–8.2)	1.7 (0.7–3.2)	0.3	–	–	–	–	–
Gastroesophageal reflux	7 (78)	134 (69)	1.6 (0.3–7.8)	1.1 (0.7–1.4)	0.7	–	–	–	–	–
Retained primary dentition*	3 (33)	1 (1)	96 (11.6–1,240)	64.3 (9.6–416)	0.0002	3 (27)	1 (0)	81 (10.2–1,048)	59.2 (8.7–387.8)	0.0003
Generalized joint hypermobility (BS ≥ 5/9)	6 (67)	101 (52)	1.9 (0.5–7.0)	1.3 (0.7–1.8)	0.5	–	–	–	–	–
Tilt-table test	2 (100)	37 (47)	≥0.5	2.1 (0.7–2.8)	0.2	–	–	–	–	–
Headache and/or migraine	6 (67)	127 (69)	0.9 (0.2–3.4)	1.0 (0.5–1.3)	>0.99	8 (73)	146 (70)	1.1 (0.3–4.1)	1.1 (0.6–1.3)	0.7
Sleep disturbances	7 (88)	106 (85)	1.2 (0.2–14.1)	1 (0.6–1.2)	>0.99	9 (90)	116 (78)	2.5 (0.4–28.0)	1.1 (0.8–1.3)	0.06
Dysphagia*	7 (78)	56 (32)	7.3 (1.5–35.4)	2.4 (1.4–3.3)	0.009	8 (73)	61 (31)	5.9 (1.7–21.1)	2.3 (1.4–3.3)	0.007
Clubfeet	0 (0)	6 (3)	0 (0.0–13.5)	0 (0.0–11.3)	>0.99	–	–	–	–	–
Chronic fatigue	9 (100)	178 (91)	≥0.2	1.1 (0.8–1.2)	>0.99	10 (91)	193 (88)	1.4 (0.2–15.7)	1.0 (0.7–1.2)	>0.99
Neurological bladder	0 (0)	5 (3)	0 (0.0–23.29)	0 (0.0–15.9)	>0.99	0 (0)	5 (2)	0 (0.7–1.0)	0 (0.0–14.7)	>0.99

BS, Beighton score; HαT, hereditary alpha-tryptasemia; hEDS, hypermobile Ehlers-Danlos syndrome; HSD, hypermobility spectrum disorder; IBS, irritable bowel syndrome; OR, odds ratio; RR, relative risk; 95% CI, 95% confidence limits; –, indicates unavailable datapoints.
*Retained primary dentition and Dysphagia rows indicate statistically significant associations.

genetic evaluations; none of these individuals were found to have a molecular genetic diagnosis for their clinical presentation(s). Among individuals with HSD only, 3.8% (5 of 132) were found to have HαT (Table S1). Similarly, 5.1% (4 of 78) of individuals diagnosed with hEDS and 7% (4 of 56) of those with axial skeletal abnormalities and hypermobility were found to have HαT. Thus, as a combined cohort, the prevalence of HαT was 4.9% (13 of 266), comparable to the prevalence established in unselected individuals (4.4%–7.5%),[1,2,4,5] indicating that HαT is not associated with these heritable connective tissue disorders.

In order to determine whether HαT might modify clinical phenotypes among individuals with joint hypermobility in a manner similar to that reported among patients with venom allergy, idiopathic anaphylaxis, and mastocytosis,[2,5] both cohorts were queried retrospectively via chart review or phone interview. Prevalence of clinical phenotypes previously associated with HαT[3] were subsequently compared based on the presence or absence of HαT (Table 1, Table S1).

Among individuals with hEDS, HαT was associated with an increased prevalence of retained primary dentition requiring surgical extraction (odds ratio [OR] ≥ 4.8; p = 0.05). Among individuals with HSD, HαT was associated with an increased prevalence of retained primary dentition (OR 79.3 [6.5–1,140]; p = 0.004) and dysphagia diagnosed by barium swallow or manometry (OR 0.2 [0.01–0.6]; p = 0.02) when compared with those without HαT. No significant differences were identified based on the presence of HαT when examining our second cohort of individuals with axial skeletal abnormalities alone (Table S1), though non-significant positive associations were observed with anaphylaxis, pruritus, and dysphagia. It should be noted that of the 56 people genotyped in this second cohort, clinical manifestations were available for only 26 of them (n = 2/4 with HαT and n = 25/52 without HαT). When individuals with hEDS and HSD were combined as a single cohort, dysphagia (OR 7.3 [1.5–35.4]; p = 0.009) and retained primary dentition (OR 96 [11.6–1,240]; p = 0.0002) remained significantly associated with HαT (Table 1). After correcting for multiple comparisons, associations between HαT and retained primary dentition (adjusted p = 0.0028) in the combined hEDS/HSD cohort, remained statistically significant. When combining genotyped individuals with hEDS, HSD, and axial skeletal abnormalities (n = 236) (Table 1), the prevalence of retained primary dentition (p = 0.0003, adjusted p = 0.004) and dysphagia (p = 0.007, adjusted p = 0.098) remained significantly increased, although only the former did when accounting for multiple comparisons.

An increased prevalence of HαT was not observed in either cohort of HSD/hEDS patients or those with axial skeletal abnormalities and joint hypermobility, where genotyping could be performed. However, as has been reported in other acquired genetic conditions,[2,5] we found that HαT was associated with a unique endotype, either due to independent association or modification of certain characteristics or clinical features in these individuals. Interestingly, the only connective tissue abnormality found previously to be significantly associated with HαT among unselected healthy adults was retained primary dentition.[3]

Whether HαT may cause clinical manifestations or modify the symptomatic presentation of other clinical disorders remains a matter of scientific debate. However, the associations seen here between HαT and retained primary dentition remained statistically significant after correcting for multiple comparisons, and are remarkably consistent with prior associations reported in both selected and unselected populations.[2-7,12,13] Interestingly, there was also an increased prevalence of anaphylaxis and pruritus among individuals with joint hypermobility and HαT, phenotypes also strongly linked to HαT in previous studies[2,3,5,7]; however, the sample size was limited, and these did not reach statistical significance when adjusting for multiple comparisons (OR 5.9 [1.1–26.0]; $p = 0.07$, adjusted $p = 0.98$) and (OR 1.9 [-0.5–6.5]; $p = 0.5$, adjusted $p > 0.99$), respectively.

While additional mechanistic work is ongoing to understand the phenotypes linked to HαT, these current data indicate that HαT is not associated with congenital joint hypermobility disorders. Additional larger studies would help confirm these findings in the future. However, given that HαT is common, it may frequently be present among individuals with such connective tissue abnormalities where it may modify and add to the diverse clinical presentations of these uniquely complex patients.

Data and code availability

The published article includes all data generated or analyzed during this study.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.xhgg.2022.100094.

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Declaration of interests

The authors declare no competing interests.

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Web resources

Online Mendelian Inheritance in Man, http://www.omim.org.

References

1. Chollet, M.B., and Akin, C. (2021). Hereditary alpha tryptasemia is not associated with specific clinical phenotypes. J. Allergy Clin. Immunol. *149*, 728–735.e2.
2. Greiner, G., Sprinzl, B., Gorska, A., Ratzinger, F., Gurbisz, M., Witzeneder, N., Schmetterer, K.G., Gisslinger, B., Uyanik, G., Hadzijusufovic, E., et al. (2020). Hereditary alpha tryptasemia is a valid genetic biomarker for severe mediator-related symptoms in mastocytosis. Blood *137*, 238–247.
3. Lyons, J.J., Yu, X., Hughes, J.D., Le, Q.T., Jamil, A., Bai, Y., Ho, N., Zhao, M., Liu, Y., O'Connell, M.P., et al. (2016). Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat. Genet. *48*, 1564–1569.
4. Robey, R.C., Wilcock, A., Bonin, H., Beaman, G., Myers, B., Grattan, C., Briggs, T.A., and Arkwright, P.D. (2020). Hereditary alpha-tryptasemia: UK prevalence and variability in disease expression. J. Allergy Clin. Immunol. Pract. *8*, 3549–3556.
5. Lyons, J.J., Chovanec, J., O'Connell, M.P., Liu, Y., Selb, J., Zanotti, R., Bai, Y., Kim, J., Le, Q.T., DiMaggio, T., et al. (2020). Heritable risk for severe anaphylaxis associated with increased alpha-tryptase-encoding germline copy number at TPSAB1. J. Allergy Clin. Immunol. *147*, 622–632.
6. Giannetti, M.P., Akin, C., Hufdhi, R., Hamilton, M.J., Weller, E., van Anrooij, B., Lyons, J.J., Hornick, J.L., Pinkus, G., Castells, M., et al. (2021). Patients with mast cell activation symptoms and elevated baseline serum tryptase level have unique bone marrow morphology. J. Allergy Clin. Immunol. *147*, 1497–1501 e1491.
7. Giannetti, M.P., Weller, E., Bormans, C., Novak, P., Hamilton, M.J., and Castells, M. (2021). Hereditary alpha-tryptasemia in 101 patients with mast cell activation-related symptomatology including anaphylaxis. Ann. Allergy Asthma Immunol. *126*, 655–660.
8. Lyons, J.J., Sun, G., Stone, K.D., Nelson, C., Wisch, L., O'Brien, M., Jones, N., Lindsley, A., Komarow, H.D., Bai, Y., et al. (2014). Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. J. Allergy Clin. Immunol. *133*, 1471–1474.
9. Sabato, V., Chovanec, J., Faber, M., Milner, J.D., Ebo, D., and Lyons, J.J. (2018). First identification of an inherited TPSAB1 quintuplication in a patient with clonal mast cell disease. J. Clin. Immunol. *38*, 457–459.
10. Frieri, M., Patel, R., and Celestin, J. (2013). Mast cell activation syndrome: a review. Curr. Allergy Asthma Rep. *13*, 27–32.
11. Vadas, P., Guzman, J., McGillis, L., Mittal, N., and Walsh, S. (2020). Cosegregation of postural orthostatic tachycardia syndrome, hypermobile Ehlers-Danlos syndrome, and mast cell activation syndrome. Ann. Allergy Asthma Immunol. *125*, 719–720.

12. Hamilton, M.J., Zhao, M., Giannetti, M.P., Weller, E., Hufdhi, R., Novak, P., Mendoza-Alvarez, L.B., Hornick, J., Lyons, J.J., Glover, S.C., et al. (2021). Distinct small intestine mast cell histologic changes in patients with hereditary alpha-tryptasemia and mast cell activation syndrome. Am. J. Surg. Pathol. *45*, 997–1004.

13. Konnikova, L., Robinson, T.O., Owings, A.H., Shirley, J.F., Davis, E., Tang, Y., Wall, S., Li, J., Hasan, M.H., Gharaibeh, R.Z., et al. (2021). Small intestinal immunopathology and GI-associated antibody formation in hereditary alpha-tryptasemia. J. Allergy Clin. Immunol. *148*, 813–821 e7.