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Patients with elevated basal tryptase serum levels should be tested for hereditary alpha-tryptasemia.

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To the editor:

Elevated total basal tryptase levels are not rare in patients presenting to allergy outpatient clinics and often lead to multiple investigations including bone marrow biopsy to exclude myeloid neoplasia and clonal mast cell diseases such as systemic mastocytosis (SM).

Hereditary alpha-tryptasemia (HAT) is a recently described inherited condition associated with elevated basal tryptase levels (1) and characterized by extra copies of the alpha tryptase encoding gene *TPSAB1*. Patients may either be asymptomatic or develop a syndrome involving multiple organ systems and characterized by symptoms similar to those of mast cell activation syndrome or CM (2). The diagnosis of HAT can be challenging and requires a careful analysis of the *TPSAB1* and *TPSB2* copy number variation (CNV). The total copy number of *TPSAB1* and *TPSB2* for normal individuals is four; individuals with a duplication in the *TPSAB1* gene have a total copy number of five or more (3).

Here we present four cases with sustained elevated basal tryptase levels without obvious explanation in whom digital droplet polymerase chain reaction (ddPCR) revealed HAT.

Case 1

A 25 year-old patient presented with an anaphylactic reaction grade 3 (according to UR Mueller (4)) following seafood ingestion. Skin testing and IgE analysis did not detect any sensitization to fish, seafood or anisakis. Total tryptase levels were elevated (17 µg/l, normal value <11.4 µg/l) initially and on several occasions in the following

years, during which the patient was in perfect health. In 2020, *TPSAB1* CNV analysis by ddPCR showed a calculated alpha-tryptase copy number of 2 and calculated beta-tryptase copy number of 3, consistent with extra allelic alpha-tryptase copies of *TPSAB1* and the diagnosis of HAT. The patient refused a bone marrow biopsy. However, based on the benign clinical course, a diagnosis of advanced SM was very unlikely.

Case 2

A 43-year-old patient presented for a grade 3 anaphylactic reaction of unknown cause. Total tryptase level was 35 µg/l. Two months later, allergic workup including skin testing and IgE analysis was inconclusive, the tryptase level was still elevated (20.5 µg/l). He complained of persistent abdominal pain, pruritic wheals and asthenia. He underwent a full work-up for suspected SM including bone marrow biopsy, next-generation sequencing for a panel of 54 genes known to be linked to hematological neoplastic disease, peripheral blood flow cytometry and c-Kit D816V mutation analysis. A panel of serologies and stool evaluation for parasites, fecal calprotectin, and gastro-duodenoscopy with biopsies were also performed (Table 1). All these investigations were unremarkable except for microcytic anemia, osteopenia and a c.1934delG, pGly345fs mutation in the *ASXL1* gene. The symptoms responded only partially to antihistaminics and cromoglicic acid, a better relief was achieved with omalizumab. A diagnosis of idiopathic mast cell activation syndrome was suspected and a close follow-up because of the *ASXL1* mutation was suggested. During the next two years, no hematological disease developed. In 2020, testing for *TPSAB1* CNV by ddPCR revealed a calculated alpha-tryptase copy number of 4 and the calculated beta-tryptase copy number was 2, consistent with the diagnosis of HAT.

Case 3

A 58 year-old HIV infected patient presented with a pruritic maculopapular erythematous rash of unknown origin. He reported having perennial rhinoconjunctivitis and throat pruritus following the ingestion of nuts. Allergic workup showed sensitization to tree pollen, grass pollen and house dust mites. Dermatological investigations ruled out cutaneous mastocytosis and were consistent with parapsoriasis. TCR rearrangement analysis did not show a clone supporting the presence of mycosis fungoides. Patch tests were negative for all suspected allergens. Phototherapy was introduced with good response. Tryptase was assessed and found increased at 17.7 µg/l. Levels were stable during four subsequent controls over the following year. *TPSAB1* CNV analysis by ddPCR showed a calculated alpha-tryptase copy number of 2 and a calculated beta-tryptase copy number of 3, consistent with HAT.

Case 4

A 53-year-old woman presented with a skin rash that occurred after administration of contrast media for a CT scan and antibiotics given for pneumonia. Skin tests with these compounds were negative. However, lymphocyte transformation test was positive for amoxicillin-clavulanic acid. Tryptase was increased in several occasions during the next year. Analysis of *TPSAB1* CNV by ddPCR revealed a calculated alpha-tryptase copy number of 3 and a calculated beta-tryptase copy number was 2, consistent with

HAT

Discussion

The four cases described here (table 1), with no familiar history of mast cell-related disease, illustrate that HAT might be more common than previously considered, as recently reported in an unselected British birth cohort where 5% had a raised *TPSAB1* copy number (3, 5). Thus, *TPSAB1* CNV should be tested in cases with elevated basal tryptase levels without obvious explanation such as end-stage kidney disease, helminth infections, and myelodysplastic/myeloproliferative disease (6). As to mastocytosis, SM in particular, a high prevalence of increased *TPSAB1* copy numbers has been reported (>15%), indicating a potential pathogenic role of HAT and an elevated risk of severe anaphylaxis (7, 8). This underscores the utility of testing for *TPSAB1* CNV in SM or in cases of severe anaphylaxis, as illustrated in our cases 1 and 2. Nevertheless, which patient qualifies for *TPSAB1* CNV testing is currently a matter of debate. HAT has been described in patients with basal tryptase levels <11.4 µg/l (2), but not <7.6 µg/l (3). On the other hand, we observed two patients exhibiting elevated basal tryptase levels of unknown origin and allergic reactions with normal *TPSAB1* copy numbers. Thus, the impact of HAT on the clinical management needs further elucidation, as increased copy numbers of *TPSAB1* seem to have a variable clinical penetrance and definitely do not rule out concomitant SM. Thus, awaiting results from larger studies on the long-term prognosis of HAT, *TPSAB1* CNV testing should not replace, but rather be added to the diagnostic work-up of elevated tryptase levels. Regarding the treatment for HAT, it becomes progressively clear that most patients will stay asymptomatic while only a minority, as case 2, will require more intensive therapy, e.g. with omalizumab, for mast cell stabilization (9).

In conclusion, the routine availability of a genetic test for HAT will help to identify a particular population of patients among those with elevated basal tryptase levels of hitherto unknown cause. The clinical significance of HAT, in particular whether these patients require a close follow-up and specific treatment due to an increased risk for severe anaphylaxis or SM, remains to be studied.

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Table 1: Patient's characteristics and digital droplet PCR results

	Clinical characteristics	Biological and radiological findings	ddPCR result
Patient 1. M, 25 yo.	Grade 3 anaphylaxis after fish consumption. No signs of cutaneous mastocytosis. Comorbidities: - Atopic dermatitis with type I sensitisation to cat and dog dander. - Ulnar compressive neuropathy.	Unremarkable peripheral blood counts and flow cytometry. No D816V c-KIT mutation in the peripheral blood. No paraprotein, negative ANA titer. Tryptase values 2018-2020: 17.1, 18.7, 16.9, 19.4 µg/l.	Calculated alpha-tryptase copy number is 2; calculated beta-tryptase copy number is 3. Total of 5 copies.
Patient 2. M, 43 yo.	Grade 3 anaphylactic reaction of unknown cause. Persistent abdominal pain, arthralgia, pruritic wheals and asthenia since the anaphylactic reaction. No signs of cutaneous mastocytosis. Comorbidities: - Depression. - No atopy. - Beta thalassemia minor.	Unremarkable thoraco-abdominal CT scan. gastroduodenal endoscopy, peripheral blood counts, bone marrow biopsy and flow cytometry no signs of parasitic infection. Osteopenia in bone densitometry. <i>ASXL1</i> gene mutation. No D816V c-KIT mutation in the peripheral blood. Tryptase values 2017-2021: 35.0, 20.5, 20.0, 23.5, 22.3, 15.5, 24.8, 16.6, 30.2, 23.6, 27.2, 26.2, 30.9 µg/l.	Calculated alpha-tryptase copy number is 4; calculated beta-tryptase copy number is 2. Total of 6 copies.
Patient 3. M, 58 yo.	Maculopapular erythematous skin lesions and pruritus of unknown origin. No signs of cutaneous mastocytosis. Comorbidities: - Allergic rhinoconjunctivitis and nut allergy. - Parapsoriasis. - HIV infection.	Normal total IgE levels, negative ANCA, normal peripheral blood cell counts, no paraprotein, no D816V c-KIT mutation in the peripheral blood. HIV1 5.6E1 copies/ml. CD4+ 482/µl. Tryptase values 2019-2020: 17.7, 17.5, 17.2, 18.8 µg/l.	Calculated alpha-tryptase copy number is 2; calculated beta-tryptase copy number is 3. Total of 5 copies.
Patient 4. F, 52 yo.	Skin rash after administration of contrast media for a CT scan. No signs of cutaneous mastocytosis. Comorbidities: - Amoxicillin-clavulanic acid allergy	Blood counts and chemistries unremarkable. No D816V c-KIT mutation in the peripheral blood. Tryptase values 2019-2020: 14.1, 15.7, 15.9 µg/l.	Calculated alpha-tryptase copy number is 3; calculated beta-tryptase copy number is 2. Total of 5 copies.

References

1. Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet.* 2016;48(12):1564-9.
2. Lyons JJ. Hereditary Alpha Tryptasemia: Genotyping and Associated Clinical Features. *Immunol Allergy Clin North Am.* 2018;38(3):483-95.
3. Robey RC, Wilcock A, Bonin H, Beaman G, Myers B, Grattan C, et al. Hereditary Alpha-Tryptasemia: UK Prevalence and Variability in Disease Expression. *J Allergy Clin Immunol Pract.* 2020;8(10):3549-56.
4. Mueller U. Insect sting allergy. Clinical picture, diagnosis and treatment. New York: Gustav Fischer Stuttgart; 1990. p. 33-5.
5. O'Connell MP, Lyons JJ. Hymenoptera venom-induced anaphylaxis and hereditary alpha-tryptasemia. *Curr Opin Allergy Clin Immunol.* 2020;20(5):431-7.
6. Valent P, Horny HP, Triggiani M, Arock M. Clinical and laboratory parameters of mast cell activation as basis for the formulation of diagnostic criteria. *Int Arch Allergy Immunol.* 2011;156(2):119-27.
7. Greiner G, Sprinzl B, Gorska A, Ratzinger F, Gurbisz W, Witzeneder N, et al. Hereditary alpha tryptasemia is a valid genetic biomarker for severe mediator-related symptoms in mastocytosis. *Blood.* 2020.
8. Lyons JJ, Chovanec J, O'Connell MP, Liu Y, Selb J, Zanotti R, et al. Heritable risk for severe anaphylaxis associated with increased alpha-tryptase encoding germline copy number at TPSAB1. *J Allergy Clin Immunol.* 2020.
9. Mendoza Alvarez LB, Barker R, Nelson C, DiMaggio T, Stone KD, Milner JD, et al. Clinical response to omalizumab in patients with hereditary alpha-tryptasemia. *Ann Allergy Asthma Immunol.* 2020;124(1):99-100 e1.