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REFERENCES

1. White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. *N Engl J Med.* 2018;379(11):1060-1070. doi:10.1056/NEJMra1712125

2. Celejewska-Wójcik N, Wójcik K, Ignacak-Popiel M, et al. Subphenotypes of nonsteroidal antiinflammatory disease-exacerbated respiratory disease identified by latent class analysis. *Allergy.* 2020;75(4):831-840. doi:10.1111/all.14141
3. Agache I, Akdis CA, Akdis M, et al. EAACI biologicals guidelines-recommendations for severe asthma. *Allergy.* 2021;76(1):14-44. doi:10.1111/all.14425
4. Sze E, Bhalla A, Nair P. Mechanisms and therapeutic strategies for non-T2 asthma. *Allergy.* 2020;75(2):311-325. doi:10.1111/all.13985
5. Pavlidis S, Takahashi K, Kee Kwong FN, et al. "T2-high" in severe asthma related to blood eosinophil, exhaled nitric oxide and serum periostin. *Eur Respir J.* 2019;53(1):1800938. doi:10.1183/13993003.00938-2018
6. Eastman JJ, Cavagnero KJ, Deconde AS, et al. Group 2 innate lymphoid cells are recruited to the nasal mucosa in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol.* 2017;140(1):101-108. doi:10.1016/j.jaci.2016.11.023

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Basal serum tryptase: A critical reconsideration of reference values

To the Editor,

The reference level of basal serum tryptase (BST) released by mast cells is still controversial because of the variability^{1,2} in the constitutive secretion of α -tryptase. Indeed, an autosomal *TPSAB1* gene replication, eventually associated with hereditary α -tryptasemia (H α T) has been observed in more than 5% of the population worldwide.^{3,4}

So far, ImmunoCAP™ Tryptase (ThermoFisher Scientific) is the only in vitro diagnostic kit available that measures total tryptase in human serum or plasma. The manufacturer has defined a 95th percentile reference level at 11.4 μ g/L but numerous studies have reported that the BST distribution in the general population is not Gaussian and that most people display BST values much lower than 10 μ g/L⁵ or even 8 μ g/L.⁶ In accordance, the manufacturer has lowered its reference value but the significance of values between 8.0 and 11.4 μ g/L still remains to be clarified.

In a preliminary retrospective study on 831 samples analyzed in one center for diagnostic purposes (681 adults; mean age 56.0 + 16.7 years; 57.8% females) confirmed that the median BST was 4.97 [2.08; 9.48] μ g/L (5th and 95th percentiles), that BST values were independent of age or gender and that they did not follow a Gaussian distribution (Table 1). Interestingly, 6 (0.9%) out of the 681 adults had a BST below the limit of detection.

This is why we intended to clarify the reference values gathering BST data measured in healthy donors (HD) in multiple laboratories. From seven independent laboratories, a total of 636 serum BST (49.3 \pm 17.9 years old, 45.6% females) was analyzed using a Phadia 250™. Median serum BST was 4.40 [2.03; 9.0] μ g/L and their distribution was not Gaussian. Seven (1.1%) BST values were greater than 11.4 μ g/L and three (0.47%) were undetectable (Table 1). Using a mathematical deconvolution analysis, we demonstrate that the distribution was made of two Gaussian curves overlapping one another

Abbreviations: BST, basal serum tryptase; FEIA, fluorimetric enzyme-linked immunoassay; HD, healthy donors; H α T, hereditary alpha tryptasemia.

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TABLE 1 Basal serum tryptase (BST) from different laboratories.

Laboratories	numbers	Sample type	Donors	Instrument	Age mean-SD (range)	BST Med [5%-95%]	F Med [5%-95%]	M Med% of M [5%-95%]	<1 µg/LNb (%)	>8 µg/LNb (%)	>11.4 µg/LNb (%)
Local	Routine	Diagnosis									
Adults	681 (82.5%)	Serum	Adults	U250	56.0 ± 16.7 (20-94)	4.97 [2.08; 17.4]	(57.8%) 4.79 [2.1; 16.6]	(42.2%) 5.47 [2.2; 17.7] NS	6 (0.9%)	147 (21.6%)	76 (11.2%)
Children teenagers	143 (17.3%)	Serum	Children teenagers	U250	10.4 ± 6.2 (0-20)	4.71 [2.14; 18.1]	(42.7%) 4.21 [2.1; 11.5]	(57.3%) 5.06 [2.2; 19.1] NS	0	26 (18.2%)	16 (11.2%)
Interlab	Healthy	Donors (HD)									
Seven labs	636	Serum	Adults	U250	49.3 ± 17.9 (18-95)	4.4 [2.0; 9.0]	(56.5%) 4.6 [2.2; 8.8]	(43.5%) 4.7 [2.0; 9.1] NS	3 (0.47%)	50 (7.9%)	7 (1.1%) [12.5-20.3]
One lab	54	Plasma	Adults	U250	NA	4.0 [1.7; 10.2] NS	NA	NA	0	6 (11.1%)	2 (3.7%) [14.9-20.0]
One lab	27	Serum	Adults	U100	55.5 ± 24.4 (18-95)	3.4 [1.9; 7.3] NS	(48.1%) 4.0 [2.0; 7.0]	(51.9%) 3.4 [1.8; 10.8] NS	0	1 (3.7%)	1 (3.7%) [17.6]
Three labs	56	Serum	Teenagers	U100 (6) U250 (50)	15.8 ± 1.62 (10-117.9)	2.6 [1.2-5.3] <i>p</i> < .001	(46.4%) 2.7 [1.2; 5.3]	(53.6%) 2.6 [1.3; 5.1] NS	0	1 (1.8%) [8.3]	0
One lab	15	Serum	Children	U100	3.9 ± 2.55 (1-9)	5.0 [3.2; 11.1] <i>p</i> = 0.0184	(20%) 5.0 [4.3-7.5]	(80%) 5.0 [3.2; -11.5] NS	0	3 (20%) [13.0]	1 (6.7%)
One lab	51	Serum	Newborns	U250	3 days	6.0 [2.5; 13.2] <i>p</i> < 0.0001	(56.9%) 5.3 [2.6-9.0] NS	(43.1%) 6.1 [4.2; 11.1] <i>p</i> = .034	0	10 (19.6%)	2 (3.9%) [11.6-13.2]

Note: First two rows: routine diagnosis BST median values in 681 adults and 143 children in a single laboratory. Last six rows BST median values performed to determine local reference value in healthy donors, in adults, dosage performed either on serum or plasma, in two different type of instruments, and in different age in children from 3 days old newborns, in 1-9 years old children, and 10-18 years old. Number of patients above the classical threshold (11.4 µg/L) or the proposed threshold (8 µg/L). Tryptase dosage was below the limit of detection of the technique (1 µg/L) in few people. Data show mean (+1 SD) or median and [5%-95%] range. Female and male results show (%) of the population before median and range. BST values according to the age are compared to the adult, Unicap 250 values while female BST values.

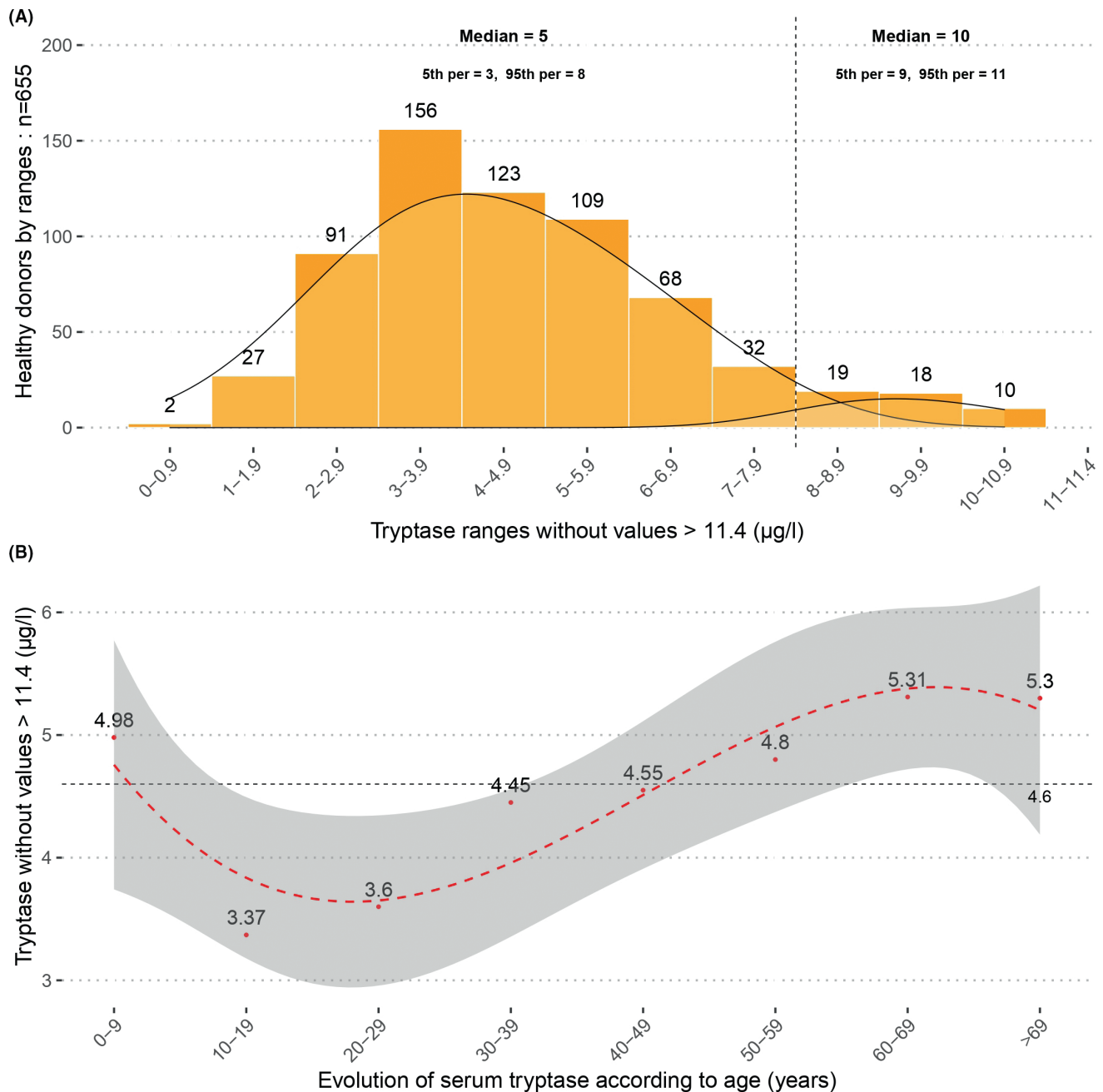


FIGURE 1 BST levels below 11.4 µg/L suggest two different subpopulations and reference values as a function of age, and (A) mathematical density curves for healthy donors suggesting two different subgroups with a normal distribution by tryptase ranges, a reference population assumed to have no TPSAB1 duplication and one of which had almost double BST values ($n=655$). Medians and percentiles (5th and 95th) of each are also shown. (B) Polynomial curve (red dashed line) representing the evolution of BST as a function of age calculated with medians (red dots) for healthy donors by age categories. The grey area on either side represents a 95% confidence interval. The median tryptase value of all healthy donors for whom age was available is also shown (black dashed line). Values with no associated age have been excluded ($n=533$).

(Figure 1A), with one centered on a median value of 5.0 [3.0; 8.0] µg/L mostly representing “low-producers” and one centered on 10.0 [9.0; 11.0] µg/L thus defining a “high-producers” (BST > 8 µg/L) represented by 50 (7.9%) HD.

We also observed that BST distribution was not significantly different when the measurement was performed on plasma (on 54 more adults, using a Phadia 250™) or on serum but using a UniCAP 100™

(on 27 more adults). Median BST was significantly lower 2.6 [1.2; 5.3] µg/L when measured in 56 healthy 10–18 years old teenagers (mean age 15.8 ± 1.62 , 46.4% female), compared to adults ($p < .001$), and tended to raise up to 5.3 µg/L in HD beyond 70 years of age. On the opposite median BST was at 6.0 µg/L [2.5; 13.2] µg/L when performed in 51 healthy 3-day-old neonates, which is significantly higher than in adults ($p < .0014$). In 10 neonates (19.6%) BST was

greater than 8 µg/L. Overall, a polynomial regression curve shows the nonlinear relationship of BST with age (Figure 1B). Individual reference remains to be referred to.

CONCLUSION

We found that the non-Gaussian distribution of BST in healthy population can be explained by a two population-model in agreement with previous works considering genetic polymorphism.^{5,6} Separating these two populations, 95% of HD display a BST below 8.0 µg/L while a minority of people had a BST > 8.0 µg/L. This latter group could be considered as "high producers" and may present gene duplication and eventually HαT, although its correlation needs to be confirmed by genetic analysis. The 95th percentile is lower in teenagers (5.5 µg/L) and slightly higher in people older than 70 years (8.5 µg/L). In addition, our data suggest that a small minority of HD has an apparent defect in basal tryptase production that needs to be explored genetically.

AUTHOR CONTRIBUTIONS

Fabien Francois, Brigitte Le Mauff, Luc de Chaisemartin, Thierry Tabary, Erwan Dumontet, Jean Claude Lecron, Benoit Delamare, Ahmed Boumediene, Angélique Chauvineau-Grenier, Remi Pescarmona, Lorna Garnier, Claude Lambert have contributed in getting the healthy donor data as well as technical conditions. Fabien Francois did the data collection and statistical analysis, bibliography, and part of writing. Louis Waeckel, Claude Lambert initiated the study, supervised the data collection, data analysis, and paper writing. Brigitte Le Mauff, Luc de Chaisemartin, Thierry Tabary, and Erwan Dumontet actively participated in paper writing.

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KEYWORDS

basal serum tryptase, hereditary alpha tryptasemia, mast cells, mastocytosis

CONFLICT OF INTEREST STATEMENT

The authors declare having no conflict of interest in this work and report.


FUNDING INFORMATION

All tryptase dosages were performed under each participating laboratory as part of certification process.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Waters AM, Park HJ, Weskamp AL, et al. Elevated basal serum tryptase: disease distribution and variability in a regional health system. *J Allergy Clin Immunol Pract.* 2022;10(9):2424.
2. Aniceto V, Dias MM, Melo JML, et al. Serum baseline tryptase level as a marker for the severity of anaphylaxis. *Int Arch Allergy Immunol.* 2019;179(3):201-208.
3. Lyons JJ. Hereditary alpha tryptasemia: genotyping and associated clinical features. *Immunol Allergy Clin North Am.* 2018;38(3):483-495.
4. Khoury P, Lyons JJ. Mast cell activation in the context of elevated basal serum tryptase: genetics and presentations. *Curr Allergy Asthma Rep.* 2019;19(12):55.
5. Komarow HD, Hu Z, Brittain E, Uzzaman A, Gaskins D, Metcalfe DD. Serum tryptase levels in atopic and nonatopic children. *J Allergy Clin Immunol.* 2009;124(4):845-848.
6. Luskin KT, White AA, Lyons JJ. The genetic basis and clinical impact of hereditary alpha-tryptasemia. *J Allergy Clin Immunol Pract.* 2021;9(6):2235-2242.