

Basal serum tryptase: a critical reconsideration of reference values

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Abbreviations:

BST: Basal Serum Tryptase **FEIA:** Fluorimetric Enzyme-Linked Immunoassay **H α T:** Hereditary α tryptasemia **HD:** healthy donors

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Author contribution

Fabien FRANCOIS¹, Brigitte LE MAUFF², Luc de CHAISEMARTIN³, Thierry TABARY⁴, Erwan DUMONTET⁵, Jean Claude LECRON⁶, Benoit DELAMARE⁷, Ahmed BOUMEDIENE⁸, Angélique CHAUVINEAU-GRENIER⁹, Remi PESCARONA¹⁰, Lorna GARNIER¹⁰, Claude LAMBERT¹

Have contributed in getting the healthy donor data as well as technical conditions

Fabien FRANCOIS¹ did the data collection and statistical analysis, bibliography and part of writing

Louis WAECKEL¹, Claude LAMBERT¹, initiated the study, supervised the data collection, data analysis and paper writing

Brigitte LE MAUFF², Luc de CHAISEMARTIN³, Thierry TABARY⁴, Erwan DUMONTET⁵ actively participated in paper writing

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“To the Editor”

The 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 has been associated with hereditary α -tryptasemia (H α T) present in more than 5% of the population worldwide³⁴.

The main manufacturer of tryptase dosage has defined a 95th percentile reference level at 11.4 μ g/L but numerous studies have reported lower levels of BST in the general population and a normal distribution. real life experience shows that most BST are much lower and some authors have adopted a reference value below 10 μ g/L⁵ or even below 8 μ g/L⁶.

This raises the epistemological question on the meaning of the “reference range” which, according to ISO15189 rules, should be included in the result report provided for diagnosis. Reference range usually consider that values have a Gaussian distribution which is not the case here, in accordance with the genetic polymorphism.

In a preliminary study on 831 dosages for diagnosis (681 adults; mean age 56.0 \pm 16.7 years; 57.8% females), the serum BST median value was 4.97 [2.08; 9.48] μ g/L (5th and 95th percentiles; FEIA “ImmunoCAP tryptase” Phadia 250; ThermoFisher Scientific, Uppsala, Sweden) and was independent of the patient age or gender but the distribution was not Gaussian (table 1). Interestingly, 6 (0.9%) out of the 681 adults had a tryptase below the limit of detection. In a prospective multicenter study gathering 636 dosages in healthy adult blood donors (HD) (49.3 \pm 17.9 years old, 45.6% females) from 7 laboratories using a Phadia 250, median serum BST was 4.40 [2.03; 9.0] μ g/L and the distribution was not Gaussian. Seven (1.1%)

BST were greater than 11.4 $\mu\text{g/L}$ and 3 (0.47%) were undetectable (**Table 1**). Using a mathematical deconvolution analysis, we were able to identify a main population with a Gaussian distribution centered on a median value at 5.0 [3.0; 8.0] $\mu\text{g/L}$ that could be considered as “low-producers”. A second population was observed with a median BST value at 10.0 [9.0; 11.0] $\mu\text{g/L}$ (**Figure 1a**). Considering this new reference range, 50 (7.9%) of the HD are “high-producers” (BST>8 $\mu\text{g/L}$).

BST was not significantly different when performed on plasma (54 tests in adults, using a Phadia 250) or in serum using a Unicap 100 (27 adults). Global median BST tended to increase with age from 2.6 [1.2; 5.3] $\mu\text{g/L}$ in 56 healthy 10-18 years old teenagers (mean age 15.8 ± 1.62 , 46.4% female), significantly lower than in adults ($p<0.001$), up to 5.3 $\mu\text{g/L}$ beyond 70 years of age. On the opposite, median BST was at 6.0 $\mu\text{g/L}$ [2.5; 13.2 $\mu\text{g/L}$] in 51 healthy 3-day-old neonates, significantly higher than in adults ($p<0.0014$), Ten (19.6%) cases had BST greater than 8 $\mu\text{g/L}$. Overall, a polynomial regression curve shows the nonlinear relationship of BST with age (**Figure 1b**) .

Conclusion

We found that the non-Gaussian distribution of BST in healthy population could be explained by a two population model in agreement with a previous work^{5,6}. A great majority has a median BST at 5.0 $\mu\text{g/L}$ and a 95th percentile at 8 $\mu\text{g/L}$. We thus propose to adopt a new threshold at 8 $\mu\text{g/L}$ and to suspect BST above 8 $\mu\text{g/L}$ as being part of the minority of healthy people with gene duplication and potentially H α T, to be confirmed by genetic analysis according to the eventual symptoms. This threshold is lower in teenagers (5.5 $\mu\text{g/L}$) and slightly higher above the age of 70 (8.5 $\mu\text{g/L}$). In addition, we describe that a small minority of HD have an apparent defect in basal tryptase production that needs to be explored genetically.

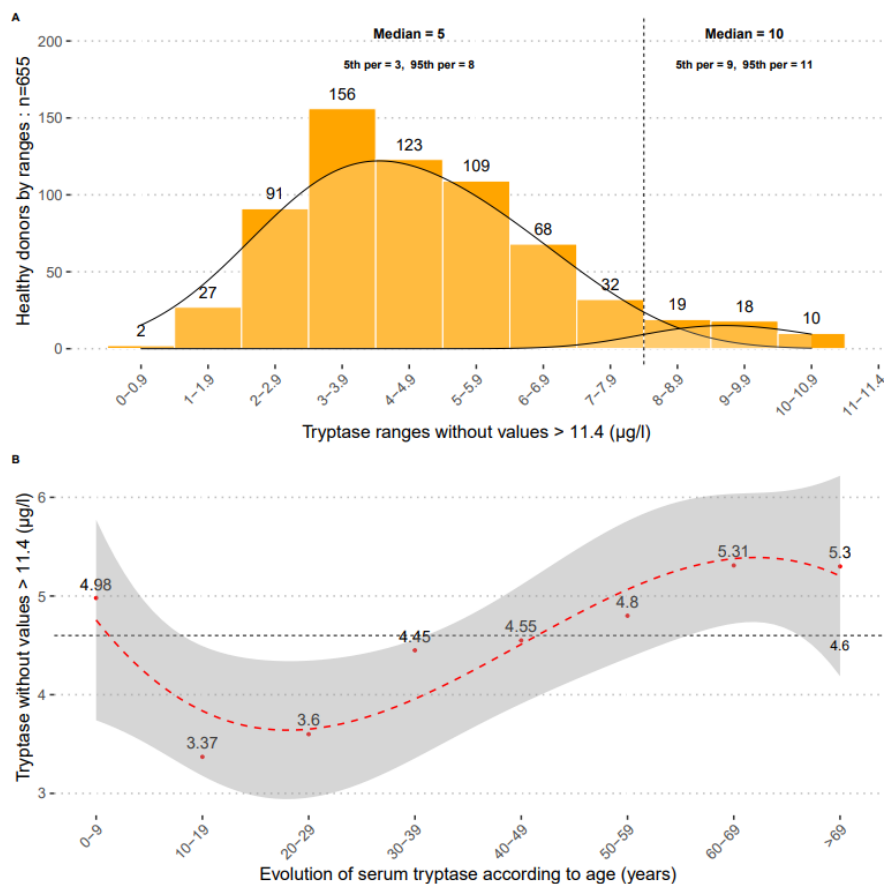
Table 1

Laboratory		Sample type		instrument	Age mean-SD (range)	BST Med [5-95 %]	F Med [5-95 %]	M Med % of M [5-95 %]	<1 $\mu\text{g}/\Lambda$ Nb (%)	>8 $\mu\text{g}/\Lambda$ Nb (%)
local	routine	diagnosis								
adults	681 (82.5%)	serum	adults	U250	56.0 \pm 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%)
children	143 (17.3%)	serum	children teenagers	U250	10.4 \pm 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%)
Interlab	healthy	donors	(HD)							
7 labs	636	serum	adults	U250	49.3 \pm 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%)
1 lab	54	Plasma	adults	U250	NA	4.0 [1.7; 10.2] NS	NA	NA	0	6 (11.1%)
1 lab	27	serum	adults	U100	55.5 \pm 24.4 (18-95)	3.4 [1.9; 7.3] NS	(48.1%) 4.0 [2.0; 7.0]	(51.9%) 3.4 [18; 10.8] NS	0	1 (3.7%)
3 labs	56	serum	teenagers	U100 (6)	15.8 \pm 1.62 (10-117.9)	2.6 [1.2-5.3] $p<0.001$	(46.4%) 2.7 [1.2; 5.3]	(53.6%) 2.6 [1.3; 5.1] NS	0	1 (1.8%) [8.3]

Laboratory		Sample type		instrument	Age mean- SD (range)	BST Med [5-95 %]	F Med [5-95 %]	M Med % of M [5-95 %]	<1μg/Λ Nb (%)	>8 μg/Λ Nb (%)
nb										
1 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] <i>NS</i>	0	3 (20%)
1 lab	51	serum	new borns	U250	3days	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] p=0.034	0	10 (19.6%)

Table 1. Basal Serum tryptase (BST) from different laboratories. First 2 rows: routine diagnosis BST median values in 681 adults and 143 children in a single laboratory. Last 6 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 μ g/L) or the proposed threshold (8 μ g/L). Tryptase dosage was below the limit of detection of the technique (1 μ g/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

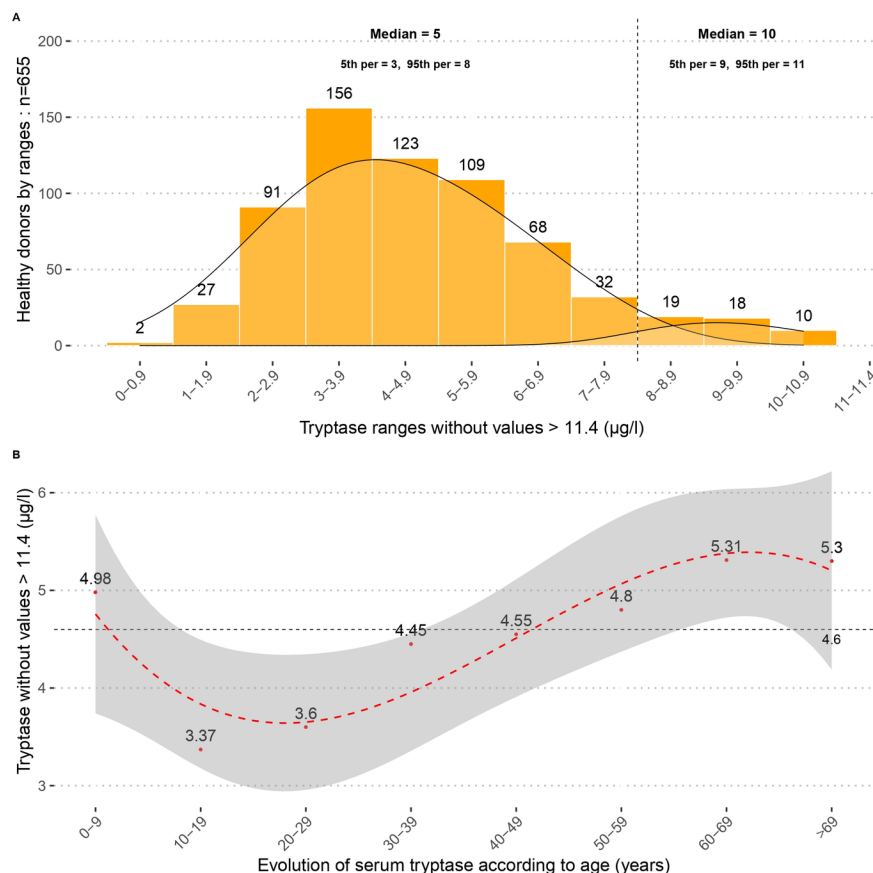
Figures



Φιγυρε 1. ΒΣΤ λееλς βελω 11.4 μγ/Λ συγγεστ τωο διφφερεντ συβποπυλατιονς ανδ ρεφερενςε αλυες ας α φυνςτιον οφ αγε, ανδ. **A** , Mathematical density curves for healthy donors suggesting 2 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).

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