TPSAB1 Copy Number Analysis by ddPCR

Last Literature Review: March 2024 Last Update: May 2024

Hereditary alpha-tryptasemia (HαT) is an autosomal dominant genetic trait that is caused by germline amplification of the alpha-tryptase isoform at the *TPSAB1* locus on chromosome 16.[1] This test uses droplet digital PCR (ddPCR) to assess for the presence of *TPSAB1* copy number variants (CNVs) and can be used in the diagnosis of HαT in individuals with consistent signs and symptoms.

Testing for *TPSAB1* CNVs may also be considered in individuals with confirmed or suspected systemic mastocytosis, Ehlers-Danlos syndrome or other connective tissue abnormalities, recurrent anaphylaxis, severe postural orthostatic tachycardia syndrome, irritable bowel syndrome, systemic venom reactions, or other systemic immediate hypersensitivity reactions.

Featured ARUP Testing

TPSAB1 Copy Number Analysis 3017399

Methodology: Droplet Digital PCR (ddPCR)

Use to confirm a suspected diagnosis of hereditary alpha-tryptasemia (HαT), rule out HαT in individuals with symptoms of mast cell activation, or as an aid in the diagnosis of systemic mastocytosis.

Disease Overview

Individuals with HαT may present with increased basal serum tryptase (≥8 ng/mL) and symptoms such as anaphylaxis, connective tissue abnormalities, dysautonomia, gastrointestinal problems, pain, and skin flushing and pruritus.[1,2,3,4] HαT may present on its own or in conjunction with mastocytosis.[3,4] Furthermore, HαT is enriched in individuals with mastocytosis.[3,4]

An elevated serum tryptase level is a minor diagnostic criterion for systemic mastocytosis according to both the World Health Organization (WHO) and International Consensus Classification (ICC), however, the WHO recommends that measurements be adjusted in individuals with HαT to properly apply the criteria.[3] There are multiple suggested methods for this adjustment; refer to the National Comprehensive Cancer Network (NCCN) guidelines for more information.[3]

Genetics

Genes

TPSAB1, TPSB2

HαT is defined by a sum of five or more total *TPSAB1*/*TPSB2* copies with at least two alpha-tryptase encoding copies of *TPSAB1*. Refer to the Possible *TPSAB1*/*TPSB2* Genotypes section for possible genetic configurations.

Inheritance

Autosomal dominant

Structure/Function

The human tryptase locus maps to 16p13.3.[2] There are four paralogous tryptase genes (*TPSG1*, *TPSB2*, *TPSAB1*, and *TPSD1*) that code for tryptase, however, the primary secreted tryptase proteins are α-tryptase (encoded by *TPSAB1*) and β-tryptase (encoded by *TPSAB1* and *TPSB2*).[2,4] Duplication and triplication of the *TPSAB1* gene (as in HαT) can result in the elevation of basal serum tryptase levels and associated risk of severe mediator symptoms (eg, anaphylaxis).[3,4]

Possible *TPSAB1*/*TPSB2* Genotypes

Possible Genotypes in Hereditary α-tryptasemia						
Allele 1 of *TPSB2* and *TPSAB1*	Allele 2 of *TPSB2* and *TPSAB1*	α-tryptase Copies	β-tryptase Copies	Total α + β	Rarity	Tryptase Concentration
β,β	β,β	0	4	4	Common	Normal
β,α	β,β	1	3	4	Common	Normal
β,α	β,α	2	2	4	Common	Normal
β,-*	β,α	1	2	3	Uncommon	Normal
β,-*	β,β	0	3	3	Uncommon	Normal
β,β	β,ββ	0	5	5	Uncommon	Normal
β,αα	β,β	2	3	5	Common	Increased
β,αα	β,α	3	2	5	Common	Increased
β,αα	β,βα	3	3	6	Common	Increased
β,αα	-,αα	4	1	5	Uncommon	Increased
β,αα	β,αα	4	2	6	Uncommon	Increased
β,ααα	β,ααα	6	2	8	Uncommon	Increased

*This assay quantifies the absolute copy numbers of α- and β-tryptase. It cannot determine whether a deletion is from the *TPSB2* or *TPSAB1* locus.

Sources: Greiner, 2021[4]

Test Interpretation

Sensitivity and Specificity

Clinical and Analytic Sensitivity and Specificity of *TPSAB1* Copy Number Analysis by ddPCR		
	Sensitivity	Specificity
Clinical	100%[1]	90% in individuals with elevated basal serum tryptase[1]
Analytic	>99%	>99%

Source: Lyons, 2016[1]

Results

Result Reported	Possible CNVs	Result Interpretation
Not increased	*TPSAB1* (0)/*TPSB2* (≤5) *TPSAB1* (1)/*TPSB2* (≤3) *TPSAB1* (2)/*TPSB2* (=2)	There is no increase in copy number of *TPSAB1* (alpha-tryptase). Calculations are based on the allelic ratio of *TPSAB1* to *AP3B1* and *TPSB2* to *AP3B1* genes.

Result Reported	Possible CNVs	Result Interpretation
Increased	*TPSAB1* (≥2)/ *TPSB2* (≥3) *TPSAB1* (≥3)/ *TPSB2* (≥2) *TPSAB1* + *TPSB2* (≥5) AND *TPSAB1* (≥2)	There is an increase in copy number of *TPSAB1* (alpha-tryptase), which is reported in HαT. Calculations are based on the allelic ratio of *TPSAB1* to *AP3B1* and *TPSB2* to *AP3B1* genes.

Limitations

- Diagnostic errors may occur due to rare sequence and CNVs.
- Single base pair substitutions, small deletions/duplications, and regulatory regions are not detected.
- This test is unable to determine chromosomal phase of *TPSAB1* and *TPSB2* genes, ie:
  - Whether *TPSAB1* copies are on the same or opposite chromosomes
  - Whether *TPSAB1* and *TPSB2* copies are on the same or opposite chromosomes
- This assay detects only the total number of *TPSAB1* and *TPSB2* gene copies by normalizing to a reference gene (*AP3B1*). Therefore, rare CNVs that affect *TPSAB1* allelic/chromosomal distribution are not detected by this assay.

References

1. Lyons JJ, Yu X, Hughes JD, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet*. 2016;48(12):1564-1569.

2. Glover SC, Carlyle A, 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.

3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Systemic mastocytosis. Version 2.2024. Published Mar 2024; accessed Mar 2024.

4. Greiner G, Sprinzl B, Górska A, et al. Hereditary α tryptasemia is a valid genetic biomarker for severe mediator-related symptoms in mastocytosis. *Blood*. 2021;137(2):238-247.

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