3-OMD TESTING FOR AADC DEFICIENCY

What is AADC deficiency?[1]

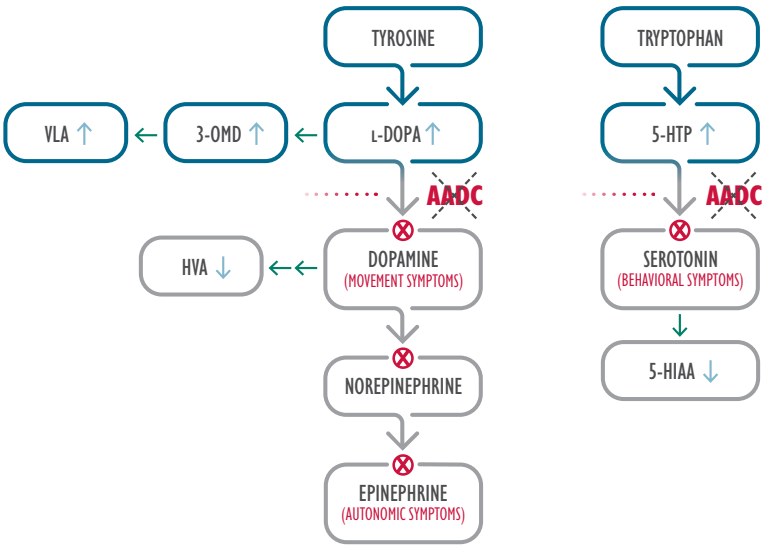
- Aromatic-L-amino acid decarboxylase (AADC) deficiency is an inborn error of neurotransmitter biosynthesis
- It is an autosomal recessive disorder caused by pathogenic variants in the dopa decarboxylase gene, *DDC*, encoding for the AADC enzyme

What is 3-OMD?[2]

- 3-O-methyldopa (3-OMD) is a more stable, catabolic product of L-DOPA
- Accumulation of L-DOPA leads to increased concentrations of 3-OMD through conversion by catechol-O-methyltransferase
- 3-OMD is detectable and stable in blood

Why is 3-OMD elevated in patients with AADC deficiency?[1,2]

- In patients with AADC deficiency, lack of AADC enzyme leads to accumulation of its substrate L-DOPA
- L-DOPA is methylated to the more stable form, 3-OMD



How does 3-OMD screening help in the diagnosis of AADC deficiency?[1-5]

Elevated levels of 3-OMD can be detected in blood

Clinical suspicion of AADC deficiency

screen for

↑ 3-OMD levels in blood

Confirm with diagnostic tests

- *DDC* full gene sequencing
- Plasma AADC enzyme activity
- CSF neurotransmitter metabolites

To diagnose AADC deficiency, genetic testing should be performed and 2 of the 3 core diagnostic tests should be positive

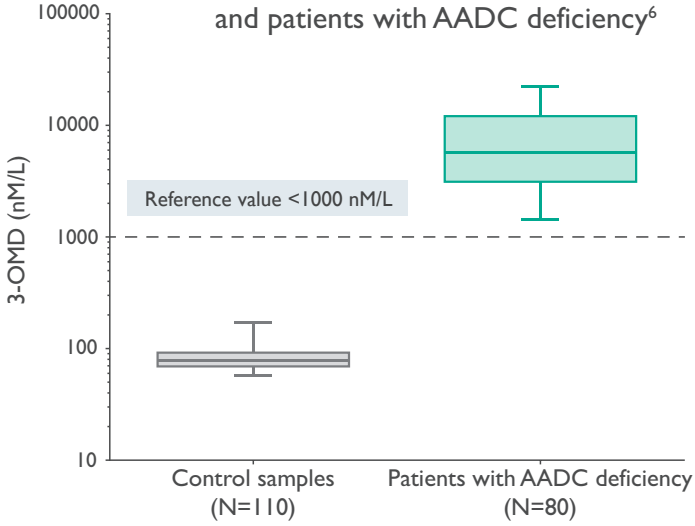
- 3-OMD can be used as an initial screen when AADC deficiency is suspected
- Elevated levels of 3-OMD in the blood should prompt further testing to confirm the diagnosis of AADC deficiency

WHY USE 3-OMD TESTING?

The 3-OMD dried blood spot assay is validated for testing in AADC deficiency[6]

- 3-OMD is increased in DBS of patients with AADC deficiency hence it is a valid and reliable biomarker for detection of AADC deficiency[3]
- In studies evaluating testing for AADC deficiency, dried blood spot testing for 3-OMD was found to have a high positive-predictive rate in newborn screening[2,3,5,a]
- CENTOGENE has performed their own validation studies in 3-OMD testing, showing 100% sensitivity and specificity of the assay in patients with AADC deficiency vs normal controls[6]

CENTOGENE study: 3-OMD concentration in dried blood spot (DBS) from controls and patients with AADC deficiency[6]



Elevated 3-OMD levels in the blood can be detected relatively easily with a simple and rapid test[2,3]

- Dried blood spot testing for 3-OMD levels is a simple, rapid, minimally invasive test used for AADC deficiency[2,3]
- Hence, it is an option for screening individuals at high risk for AADC deficiency and a potential option for newborn screening[2,5]
- This test may aid early diagnosis of AADC deficiency and help to bridge the delay (typically months to years) in the diagnosis of the disease[1,5]

Screening for elevated 3-OMD in the blood of patients with suspected AADC deficiency may aid in early diagnosis[5]

Partnership with CENTOGENE

CENTOGENE
THE RARE DISEASE COMPANY

- PTC has partnered with CENTOGENE to offer 3-OMD testing via dried blood spot for initial screening of patients in whom AADC deficiency is clinically suspected and/or in at-risk patient populations[4]
- For additional information, contact **AADCDtesting@ptcbio.com**

[a]In one study, one newborn had a false positive; investigations showed the mother was on L-DOPA therapy during pregnancy.[3]

Abbreviations: GC-MS, gas chromatography mass spectrometry; L-DOPA, L 3,4 dihydroxyphenylalanine; CSF, cerebrospinal fluid; DBS, dried blood spot; 3-OMD, 3-O-methyldopa; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HTP, 5-hydroxytryptophan; HVA, homovanillic acid; VLA, vanillactic acid.

References: 1. Wassenberg T, et al. *Orphanet J Rare Dis.* 2017;12(1):12. doi:10.1186/s13023-016-0522-z. **2.** Chen PW, et al. *Clin Chim Acta.* 2014;431:19-22. **3.** Brennenstuhl H, et al. *J Inherit Metab Dis.* 2019;doi:10.1002/jimd.12208. **4.** Hyland K, Reott M. *Pediatr Neurol.* 2020;106:38-42 **5.** Chien YH, et al. *Mol Genet Metab*. 2016;118(4):259-263. **6.** Data on file. CENTOGENE AG. 2019

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