Title: Ongoing Clinical Validity Assessment Leads to Efficient Genetic Test Development for Patients with Movement Disorders and Hypotonia

Authors: Meghan C. Towne, Devon Thrush, Haley Keller, Bess Wayburn, Jeffrey Kopesky, Ryan Miller, Deepali Shinde, Benjamin Feldmann, Kelly Hagman, Kelly Radtke

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare neurometabolic disorder that results in a decrease in the biosynthesis of several neurotransmitters due to *DDC* alterations. Most patients have early-onset severe disease, but there are reports of mild to moderate presentations. AADC deficiency can present similarly to other conditions. While diagnosis may be suspected from clinical features, it must be confirmed by assessing AADC activity, cerebrospinal fluid metabolites, or by genetic testing.

We (1) established criteria for a phenotype-driven diagnostic program by categorizing the differentiating features of AADC deficiency and (2) utilized an internal clinical validity database to identify relevant genes for a multigene panel (MGP).

We discerned the core features of AADC deficiency and differential diagnoses by reviewing the literature and speaking to 5 neurometabolic specialists representing neurologists, genetic counselors, and geneticists. Clinical inclusion criteria for participation in the program were defined as congenital hypotonia with extrapyramidal (EP) movement disorder +/- other neurological or autonomic features.

Our laboratory scores the clinical validity strength of gene-disease associations into a curated database on an ongoing basis. To assess gene relevance for inclusion on a MGP targeting AADC deficiency, genes associated with congenital hypotonia or EP movement disorders were selected and further narrowed by clinical relevance. Genes associated with late-onset disease, brain malformations, leukodystrophies, or other features not typically in AADC differential diagnoses considerations were removed. Disorders that present with dyskinetic cerebral palsy were given special consideration and protected. 460 genes associated with movement disorders were narrowed to 81 relevant genes for inclusion on the MGP.

Clinician education on accurately identifying the features of AADC deficiency and ordering appropriate genetic testing is crucial for optimizing patient outcomes. Clear inclusion criteria and comprehensive clinical validity data are critical for developing quality MGP and reducing variants of uncertain significance. Sponsored phenotype-drive diagnostic programs enhance awareness for rare disorders and promote equitable access to genetic testing by removing payment barriers.

COI Declaration

Meghan Towne, Devon Thrush, Haley Keller, Bess Wayburn, Deepali Shinde, Benjamin Feldmann, Kelly Hagman, and Kelly Radtke are salaried employees of Ambry Genetics, a Konica Minolta Company. Jeffrey Kopesky and Ryan Miller are salaried employees of PTC Therapeutics Inc. The panel described in this abstract was developed in paid partnership between Ambry Genetics and PTC Therapeutics.

References used, but not included in the abstract (no place to include them in the submission form)

1. Pearson, T.S., et al., *AADC deficiency from infancy to adulthood: Symptoms and developmental outcome in an international cohort of 63 patients.* J Inherit Metab Dis, 2020. **43**(5): p. 1121-1130.
2. Wassenberg, T., et al., *Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency.* Orphanet J Rare Dis, 2017. **12**(1): p. 12.
3. Kojima, K., et al., *Gene therapy improves motor and mental function of aromatic l-amino acid decarboxylase deficiency.* Brain, 2019. **142**(2): p. 322-333.
4. Himmelreich, N., et al., *Aromatic amino acid decarboxylase deficiency: Molecular and metabolic basis and therapeutic outlook.* Mol Genet Metab, 2019. **127**(1): p. 12-22.
5. Smith, E.D., et al., *Classification of Genes: Standardized Clinical Validity Assessment of Gene-Disease Associations Aids Diagnostic Exome Analysis and Reclassifications.* Hum Mutat, 2017. **38**(5): p. 600-608.