# Arginase 1 Deficiency (ARG1-D) Presenting With Clotting Abnormalities

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## Introduction and Objective
- Arginase 1 Deficiency (ARG1-D) is a rare, debilitating inherited metabolic disease with significant morbidity driven by persistent high arginine levels.
- Disease manifestations typically begin to develop in early childhood and progress over time:
  - Progressive spasticity, most commonly affecting the lower limbs, is a hallmark of ARG1-D.
  - Other common manifestations include seizures, intellectual disability, developmental delay, and failure to thrive.
  - Patients may also exhibit food avoidance and/or vomiting.
- Early detection and treatment of ARG1-D is essential for delaying or decreasing progression and has been shown to have a positive impact on patient outcomes later in life.
- The aim of this presentation is to describe a patient with ARG1-D who presented with an atypical profile and was definitively diagnosed through whole-exome sequencing 2 years after initial presentation.

## Presentation and Initial Assessments
- The patient is a female of Hispanic descent who presented to acute care at 3 years of age because of new-onset seizures.
  - Upon admission, global developmental delay, intellectual disability, failure to thrive, and proteinuria were evident.
  - No seizures and prolonged prothrombin time prompted referral to hematology for further evaluation.
- Several abnormalities were detected during workup (Table 1). Vitamin K deficiency was considered but the patient's prolonged prothrombin time did not decrease upon oral or subcutaneous vitamin K administration.
  - Suspicions of a vitamin K receptor disorder prompted referral to genetics.

## Diagnosis
- Time from presentation to diagnosis was nearly 2 years owing to a combination of the patient's presentation and access to testing (Figure 1):
  - An inborn error of metabolism (IEM) was not high on the differential at this time due to the patient's biochemistry and history of normal newborn screens.
  - Based on access, chromosomal microarray and gene panels for congenital disorders of glycosylation and comprehensive glycogen storage disease panels were ordered; results did not suggest a diagnosis.
  - Whole-exome sequencing ultimately revealed a homozygous pathogenic variant in *ARG1* (c.466G>C) indicating a diagnosis of ARG1-D. Amino acid testing confirmed the ARG1-D phenotype (plasma arginine, 607 μmol/L; reference range, 18–127 μmol/L).

## Figure 1: Diagnostic Journey

<table>
<thead>
<tr>
<th>2010</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (ARG1-D not on panel)</td>
<td>Single gene testing and/or WES (access restricted)</td>
<td>Long contiguous regions of homozygosity (chromosomes 5 &amp; 6)</td>
<td>DDHA (heterozygous VUS)</td>
</tr>
<tr>
<td>NBS</td>
<td>Medical Genetics</td>
<td>Chromosomal microarray ordered</td>
<td>High αPiA</td>
</tr>
<tr>
<td>NBS</td>
<td>Hematology</td>
<td>Presented</td>
<td>AA panel</td>
</tr>
<tr>
<td>Birth</td>
<td>Presentation</td>
<td>(based on access)</td>
<td>Genes panels ordered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(continued restricted access to WES)</td>
<td>ARG1 (homozygous pathogenic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Definitive ARG1-D diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SOR initiated</td>
</tr>
</tbody>
</table>

*References: NBS, newborn screening; αPiA, plasma α1-antitrypsin; SOR, standard of care; VUS, variant of unknown significance; WES, whole-exome sequencing.*