

## Adenylosuccinase (*ADSL*) Gene Sequencing – Test #564

**Brief Description of Clinical Features:** The Adenylosuccinase enzyme (*ADSL*) carries out two independent steps of purine biosynthesis (Van Keuren et al. *AJHG* 39:172, 1986; Van Keuren et al. *Cytogenet Cell Genet* 44:142-147, 1987). Adenylosuccinase deficiency [OMIM 103050] is characterized by the accumulation of succinylamino-imidazole carboxamide riboside (SAICAr) and succinyladenosine (S-ado) in cerebrospinal fluid and urine (Jaeken and Van den Berghe, *Lancet* 324:1058-1061, 1984). *ADSL* deficient patients usually present with moderate to severe intellectual disability, often accompanied by epilepsy and/or autistic features (poor eye contact, repetitive behavior, temper tantrums). *ADSL* deficiency occasionally presents with growth retardation and muscular hypotonia. Type 1 *ADSL* deficiencies are associated with severe to moderate psychomotor retardation, epilepsy, and/or autism; type 2 cases present milder forms of these symptoms. The most severe cases manifest as generalized seizures starting within the first days or weeks of life, leading to death within a few months.

**Genetics:** Adenylosuccinase deficiency is a rare autosomal recessive disorder caused by mutations in the *ADSL* gene located on chromosome 22q13.1-q13.2 (Van Keuren et al. *Cytogenet Cell Genet* 44:142-147, 1987; Fon et al., *Cytogenet Cell Genet* 64:201-203, 1993). Although a few chain-termination mutations have been reported, the great majority of causative *ADSL* mutations are missense resulting in amino acid substitutions (Gitiaux et al. *Eur J Hum Genet* 17:133-136, 2009). One of the most common is c.1279G>A resulting in p.Arg426His.

**Description of This Particular Test:** This test involves bidirectional DNA sequencing of all 13 exons of the *ADSL* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence one (Test #100) or two (Test #200) exon(s) in family members of patients with a known mutation or to confirm research results (\$190/\$340).

**Reference Sequences:** Genomic: NC\_000022.10 mRNA: NM\_000026.2 Protein: NP\_000017.1 (CCDS\_14001.1)

**Indications for Test:** Candidates for this test are patients with elevated levels of SAICAr or S-ado, at 100-500 µM concentration in cerebrospinal fluid, or 25-700 µmol/mmol of creatinine in urine (Stone et al., *Nature Genet* 1:59-63, 1992). In addition, testing for Adenylosuccinase deficiency has also been recommended in patients with mental retardation and a behavioral profile suggestive of Angelman syndrome (Gitiaux et al. *Eur J Hum Genet* 17:133-136, 2009).

**Sensitivity of Test:** All of the currently documented *ADSL* causative mutations are detectable by sequencing (<http://www.hgmd.cf.ac.uk/>). However the possibility of large deletions and other mutations which are not detectable by our sequencing test cannot be discounted. Due to the marked heterogeneity of clinical features, the overall prevalence of *ADSL* deficiency is currently unknown.

**Turnaround Time:** Maximum of 40 calendar days, although many tests are completed in 3-4 weeks.

**Specimen Requirements:** See page 4 of Requisition Form.

<b>Price:</b>	<b>Sequencing of the <i>ADSL</i> Gene:</b>	<b>\$ 860</b>
<b>CPT Codes:</b>		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x17	83898 \$ 240	Sequencing x17 83904 \$ 360
Separation x1	83894 \$ 70	Interpretation/Report x1 83912 \$ 120

**Accreditation Info:** CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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