

## *PUS1* Gene Analysis in Mitochondrial Myopathy, Lactic Acidosis and Sideroblastic Anemia (MLASA)

### **Clinical Features:**

Mitochondrial myopathy, lactic acidosis and sideroblastic anemia (MLASA) is a rare disorder of oxidative phosphorylation that presents in childhood and is characterized by muscle weakness, normocytic anemia and lactic acidemia. Other features that have been described in affected individuals include microcephaly, micrognathia, high philtrum, high palate, intellectual disability, and growth hormone deficiency.<sup>1</sup> Survival into adulthood has been described in two individuals, including one male with chronic sideroblastic anemia, diarrhea, microcephaly and failure to thrive presenting in childhood, and moderate muscle weakness occurred in adulthood<sup>2</sup>, and one female presenting with mild cognitive impairment and sideroblastic anemia since childhood, and later developed hepatopathy, cardiomyopathy, and insulin-dependent diabetes, thus expanding the clinical spectrum of MLASA.<sup>3</sup> Variability in clinical features has been described even within members of the same family.<sup>1</sup>

### **Inheritance:**

Autosomal recessive

### **Genetics:**

MLASA is caused by pathogenic variants in the *PUS1* that encodes a tRNA pseudouridine synthase that converts uridine into pseudouridine at several tRNA positions in both nuclear and mitochondrially encoded tRNAs. Pseudouridylation is the most frequently found modification in tRNAs and seems to increase the efficiency of protein translation.<sup>1</sup> Defective pseudouridylation of tRNAs is believed to lead to impaired translation of nuclear and mitochondrial genes involved in mitochondrial metabolism and ultimately to altered oxidative phosphorylation.<sup>4</sup> The *PUS1* gene is located on chromosome 12q24.33 and has 6 exons.

### **Test Methods:**

Variant analysis of the *PUS1* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *PUS1* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

## Test Sensitivity:

In a study of 60 probands with congenital sideroblastic anemia, one novel homozygous nonsense variant in the *PUS1* gene was identified in one individual and a homozygous founder variant in the *PUS1* gene was identified in another proband.<sup>4</sup> To our knowledge, a large study of the frequency of *PUS1* variants in patients recognized as having MLASA has not been published. The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

## Variant spectrum:

At this time, very few variants in the *PUS1* gene have been reported most of which are missense or nonsense variants. A founder mutation (p.Arg144Trp or R144W) has been identified in persons of Persian Jewish descent.<sup>5</sup> A homozygous 6-kb deletion in the *PUS1* gene has been reported in two individuals with MLASA.<sup>6</sup>

## References:

1. Fernandez-Vizarra et al., (2007) J Med Genet 44:173-180 (PMID: 17056637).
2. Metodiev et al. (2015) Eur. J. Hum. Genet. 23 (6):880-2 (PMID: 25227147).
3. Cao et al. (2016) Neurogenetics 17 (1):65-70 (PMID: 26556812).
4. Bergmann et al., (2010) Pediatr Blood Cancer 54:273-278 (PMID: 19731322).
5. Bykhovskaya et al., (2004) Am J Hum Genet 74:1303-1308 (PMID: 15108122).
6. Tesarova et al. (2018) Pediatr Blood Cancer :e27591 (PMID: 30588737).