

## *PSAP* Gene Analysis in *PSAP*-Related Disorders

### **Disorders Included:**

Prosaposin Deficiency

Krabbe Disease due to Saposin A Deficiency

Metachromatic Leukodystrophy due to Saposin B Deficiency

Gaucher Disease due to Saposin C Deficiency

### **Clinical Features:**

Pathogenic variants in the *PSAP* gene have been associated with prosaposin deficiency, Krabbe disease, metachromatic leukodystrophy and Gaucher disease.

There have been only a few reports of patients with prosaposin deficiency all of whom were described as having a severe neurovisceral storage disease that was evident at birth with a rapidly fatal course.<sup>1, 2, 3</sup> Hypotonia, hepatosplenomegaly, myoclonic jerks, abnormal ocular movements, dystonia and seizures were also described.<sup>1, 2, 3</sup>

At this time, only a single patient has been described with Krabbe disease due to saposin A deficiency. This patient had dysmyelination of the cerebral white matter with a very rapid neurological deterioration that ended in death at eight months.<sup>4</sup>

Most patients with metachromatic leukodystrophy due to saposin B deficiency have presented with the late infantile form in which symptoms appear between the ages of 1 to 2 years with neuroregression, walking difficulties, dysarthria and lower limb spasticity.<sup>5</sup> Patients with the juvenile-onset and adult-onset forms have also been described.<sup>5</sup> In Saudi Arabia metachromatic leukodystrophy due to saposin B deficiency appears to be more common than the classic arylsulfatase A-deficient metachromatic leukodystrophy.<sup>5</sup>

The majority of patients with Gaucher disease due to saposin C deficiency have most often been described as having type 3 (subacute or chronic neuronopathic) Gaucher disease that is characterized by severe systemic involvement and supranuclear saccadic horizontal gaze palsy, with or without developmental delay, hearing impairment and other brainstem deficits, or a relatively mild systemic disease but with progressive myoclonic encephalopathy, seizures, dementia and death.<sup>6, 7</sup> However, patients with saposin C deficiency who have the more common type 1 Gaucher disease presentation have also been reported.<sup>6, 8</sup>

### **Inheritance Pattern/Genetics:**

The *PSAP* gene encodes the prosaposin protein (pSap), a precursor of four small non-enzymatic glycoproteins that are required to activate the lysosomal degradation of

glycosphingolipids. Pathogenic variants in the *PSAP* gene can result in a deficiency of either the entire pSap protein, resulting in prosaposin deficiency, or an individual saposin resulting in SapA, SapB or SapC deficiency. Each saposin is an activator of a specific lysosomal hydrolase, and the deficiency of SapA, SapB or SapC results in the loss of the corresponding enzyme activity *in vivo*.<sup>8</sup> *In vitro* enzyme activities using artificial substrates do not reflect the level of decreased activity in patient tissues. SapA is required for the degradation of galactosylceramide, SapB is necessary for the lysosomal degradation of sulfatides and SapC is required for the degradation of glucosylceramide.<sup>4, 5</sup> To date, isolated SapD deficiency has not been described in humans.<sup>2</sup> In addition to its role as a precursor of saposin proteins involved in sphingolipid hydrolysis, pSap has been shown to have other properties including neurotrophic and regenerative effects.<sup>1</sup> The *PSAP* gene is located on chromosome 10q22.1 and has 14 exons. *PSAP*-related disorders are inherited in an autosomal recessive manner.

### Test Methods:

Variant analysis of the *PSAP* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of the coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *PSAP* 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:

There are no large studies of patients with a deficiency of pSap, SapA, SapB or SapC; therefore, sensitivity of this test, as described above, for detecting variants in the *PSAP* gene in affected individuals cannot be established at this time. In the majority of reported patients, variants in both *PSAP* alleles were identified by sequence analysis.<sup>1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13</sup>

*PSAP* variants consist of missense, nonsense, splicing and small deletions. The majority of patients with a deficiency of pSap are homozygous for single variants.<sup>1, 2, 3, 4, 5, 9, 10, 11, 12</sup>

Patients with prosaposin deficiency have variants that result in the complete loss of functional pSap and SapA-D.<sup>2</sup> Patients with deficiencies of a single SAP may be homozygotes or compound heterozygotes for variants that effect a specific SAP, or they can be compound heterozygotes for a variant that effects a single SAP and a null pSap variant.<sup>2</sup> In Saudi Arabia, four unrelated families have been reported with metachromatic leukodystrophy due to saposin B deficiency with the same homozygous variant (p.Cys241Ser).<sup>5</sup> Most *PSAP* variants have only been described in a single family.

## References:

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