

Practical guidelines for molecular testing in hereditary spastic paraplegia

Disease definition : Hereditary spastic paraplegia (HSP, Strumpell's disease).

Frequency : The frequency of HSP is estimated at 1-2 in 100.000.

Main clinical symptoms : HSP is characterized by progressive spasticity with increased muscle tone, hyperreflexia, extensor plantar responses, muscle weakness and atrophy, sensory disturbances of the lower extremities and neurogenic bladder disturbances.

Inheritance : HSP can be inherited in an autosomal dominant, autosomal recessive or X-linked manner. Most non-syndromic HSP is autosomal dominant.

Clinical diagnosis : HSP is a clinical diagnosis. Pathologic examination may show axonal degeneration and demyelination at the distal ends of the corticospinal tracts, but is rarely performed.

Clinical classification : HSP is uncomplicated or non-syndromic if spastic paraplegia is the only symptom. It is complicated or syndromic if accompanied by other symptoms, most frequently other neurologic symptoms including seizures or dementia. Although the 2 genes most commonly mutated in HSP, SPG3A and SPG4, usually lead to non-syndromic spastic paraplegia, many HSP entities clearly are syndromic or mixed syndromic/non-syndromic.

Molecular testing : Up to now more than 30 loci with 15 nuclear genes have been shown to be implicated in non-syndromic HPS. All loci have been classified as SPG (for Spastic Paraplegia gene), followed by a number indicating the chronological order of identification of the locus.

- **Autosomal Dominant HSP :** 9 genes have been shown to cause autosomal dominant HSP, including SPG4, SPG3A, NIPA1, KIF5A, KIAA0196, HSPD1, BSCL2, REEP1, and ZFYVE27. SPG4 mutations account for 40-50 % of all autosomal dominant HSP, with deletions (not detectable by sequencing or DHPLC) being as frequent as point

mutations or small truncating mutations. SPG3A is responsible for about 10% of autosomal dominant HSP.

- **Autosomal recessive HSP** : 5 genes have been shown to cause autosomal recessive HSP : paraplegin (SPG7), KIAA1840 (SPG11), spastizin/ZFYVE26 (SPG15), spartin (SPG20), and maspardin (SPG21).
- **X-linked HSP** : Apart from SPG16, no real X-linked nonsyndromic HSP has yet been identified. SPG1 caused by mutations in L1CAM encoding the neural cell adhesion molecule L1 is syndromic as it always associated with mental retardation and other anomalies. SPG2 caused by mutations in PLP1 encoding myelin proteolipid protein can manifest as non-syndromic HSP. Mutations in another X-linked gene ALD can lead to non-syndromic HSP, apart from the classical phenotype of adrenoleucodystrophy.

References

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Table 1. Different types of non-syndromic HSP with the proportion of the respective gene, its size, price indication, and test advise.

Type	Gene	Protein	Relative gene contribution	Number of Exons (AA)	Price indication (Euro)	Test Advise
Autosomal dominant	SPG4	Spastin	40 %	17 exons (616 AA)	1000	Test 1
	SPG3A	Atlastin	10 %	13 exons (553 AA)	1000	Test 2
	various	Various	< 3 %	Various	Various	No test advised
Autosomal recessive	various	Various	< 3 %	Various	Various	No test advised
X-linked	Various	Various	< 3 %	Various	Various	No test advised