

# Heterogeneity of Hereditary Spastic Paraplegia and the finding of phenotypic modifier variants - Implications for genetic testing and clinical management



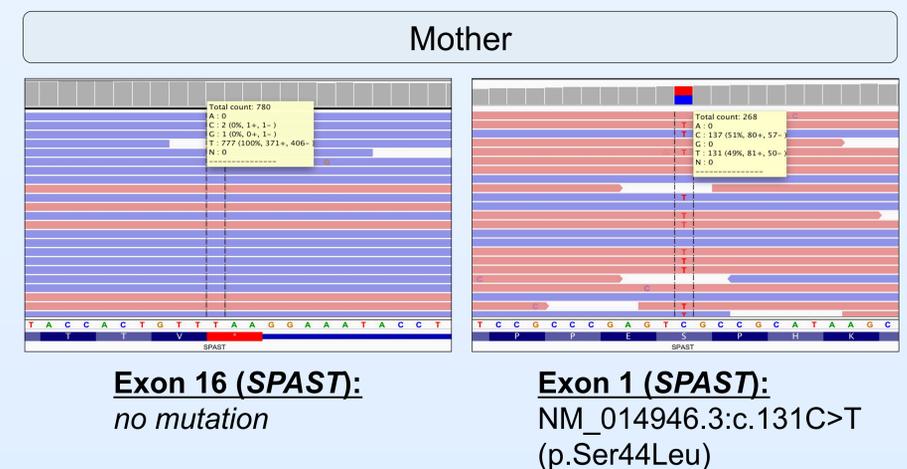
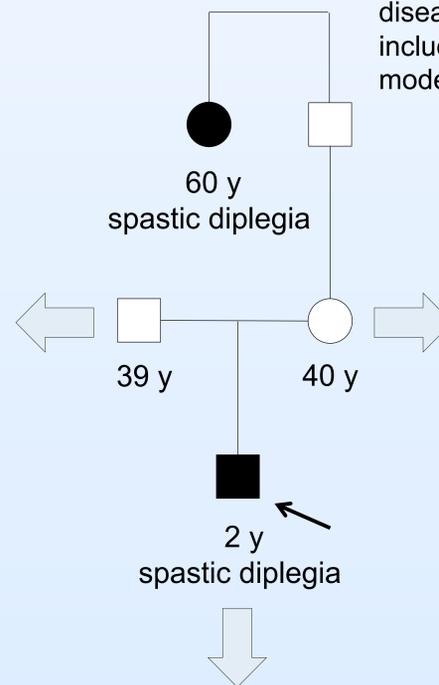
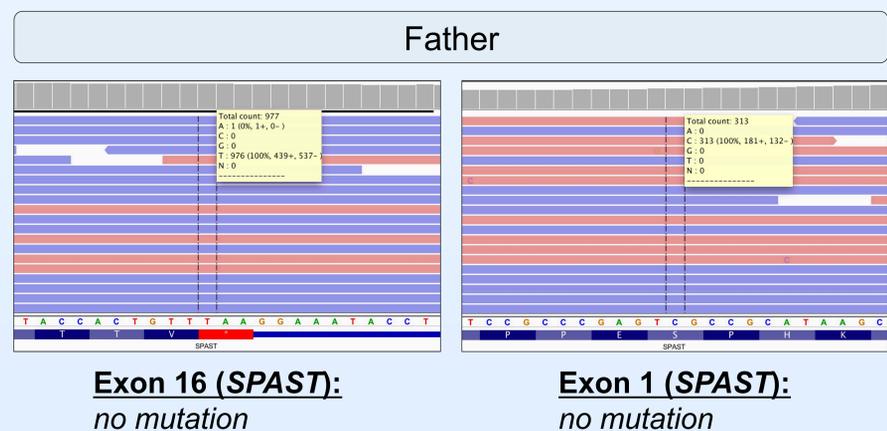
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## Introduction

The hereditary spastic paraplegias (HSP) are a heterogeneous group of inherited disorders characterized by progressive spasticity and weakness affecting the lower extremities. Most cases of pure HSP are autosomal dominant (AD), whereas complicated forms tend to be autosomal recessive. Around 70-80% of the pure, autosomal dominant HSP are caused by mutations in the three genes *SPAST* (SPG4), *ATL1* (SPG3A), and *REEP1* (SPG6). SPG4 is the most common HSP. Although age at onset of SPG4 is variable, manifestations are usually not recognized until early adulthood, whereas SPG3A is the most frequent cause of HSP with onset in early childhood. Genetic testing in pure HSP is guided by the known prevalence of mutations, age of onset and family history. Despite this, devising a time and cost efficient testing strategy for HSP can be complex, costly and time consuming due to their clinical variability, large and increasing number of known HSP loci, and the possible role of genetic modifiers.

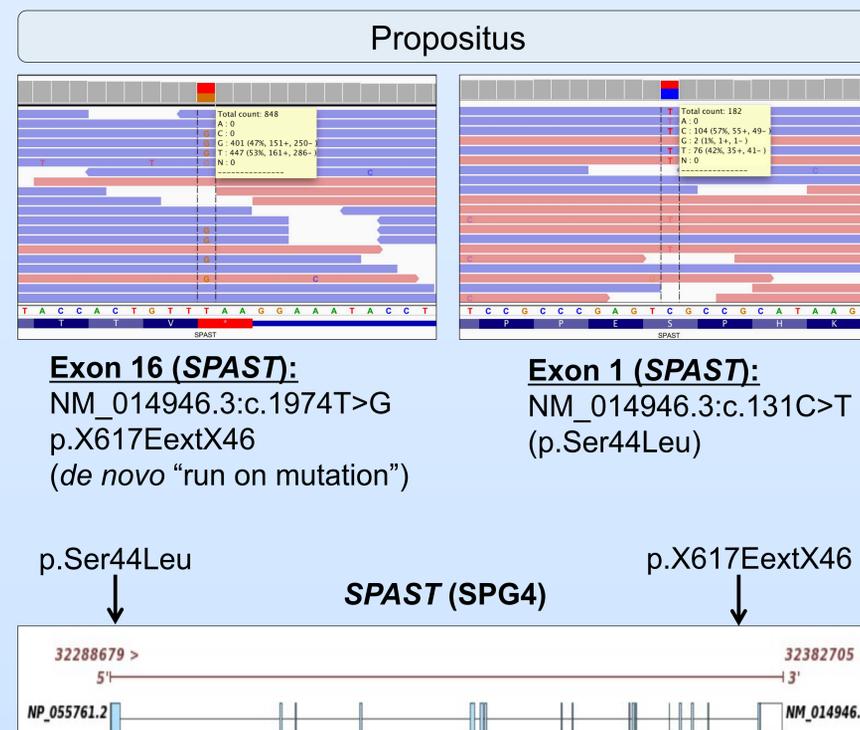


## Discussion

- Contrary to the common perception, SPG4 can present in infancy and sequencing should not stop after one pathogenic mutation has been identified, particularly if the phenotype is severe.
- The missense mutation S44L is identified at low frequencies in control populations
- S44L is thought to act as phenotypic modifier resulting in a more severe phenotype of HSP when present in addition to another mutation in the spastin gene.
- However, the pathogenic contribution of S44L may be more complex:
  - The homozygous presence of S44L has been described in adult-onset spastic paraplegia
  - Individuals heterozygous for S44L have been documented to have abnormal EMGs
  - *SPAST* has recently been shown to interact in a gene interaction network with other genes causing HSP and various other neurodegenerative diseases.
  - Common etiological pathways within HSP and between different neurodegenerative diseases suggest that the pathogenic contribution of mutations in HSP genes including S44L may depend on the context of both common low penetrance and rare moderate to high penetrance variants.

## Case

A 2-year-old boy presented with spastic diplegia previously diagnosed as “cerebral palsy”. Although both parents were asymptomatic, the maternal family history was significant for a maternal great-aunt (see pedigree) as well as another distant maternal relative (not shown) with spastic diplegia suspected to have “cerebral palsy”. An HSP panel ordered at an outside institution revealed a “run on mutation” (p.X617EextX46) in the *SPAST* gene. No large deletions in *SPAST*, or mutations in *ATL1* and *REEP1* were found. Neither parent was a carrier of the *SPAST* mutation. However, sequencing of both parents revealed a variant (p.S44L) in the maternal *SPAST* gene. NGS re-sequencing of the child confirmed presence of the maternal p.S44L variant, which was not reported with the initial HSP panel, in addition to the previously found mutation in *SPAST*.



## Conclusion

- Sequencing large number of genes once and allowing for the flexible query of gene panels tailored to the clinical situation with the option of broadening the search through subsequent queries may help optimizing cost and time efficiency for conditions with a high degree of clinical and genetic heterogeneity and large numbers of genes involved.
- Further family studies to determine the role of the S44L variant and possible other genetic factors include EMG studies of the mother (EMG) and genetic studies in the maternal grand aunt with spastic diplegia.

## References

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3. Svenson IK *et al.* Neurogenetics. 2004 Sep;5(3):157-64.