Diagnostic challenges in hereditary spastic paraplegia: genetic analysis of a large cohort of Portuguese patients

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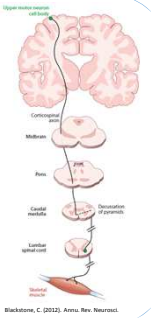
Introduction

Hereditary spastic paraplegia (HSP):

- heterogeneous group of neurodegenerative disorders characterized by slowly progressive lower limb spasticity and weakness that can be complicated by other neurological or non-neurological features.
- pathologically characterized by axonal degeneration of the longest nerve fibers in the corticospinal tracts.
- estimated prevalence is of 3-10/100,000 in Europe.
- four modes of genetic inheritance described and more than 70 identified loci.
- despite this high number of identified genes, approximately 40 to 70% of the families persist without molecular diagnosis.



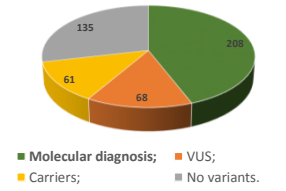
Aim and strategy

Molecular diagnosis of 472 HSP patients (probands)

- Single-gene tests
- Whole-exome sequencing based multigene panels

Cohort results

Total of patients (n=472)

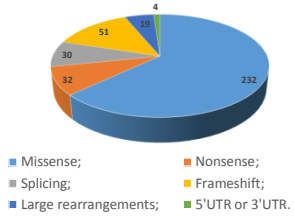


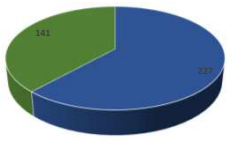
Single-gene tests → 118 patients (with molecular diagnosis)

Whole-exome sequencing based multigene panels → 90 patients (with molecular diagnosis)

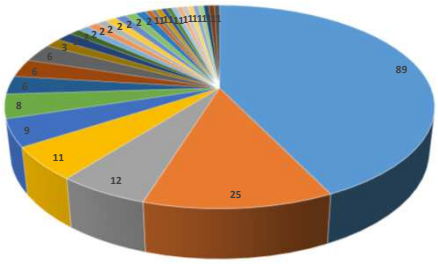
208 patients

Total of different variants identified (n=368) in 87 genes





164 different disease-causing variants identified in 33 genes



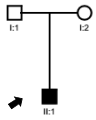
SPAST (42,8%); *SPG11 (12%);* *SPG7 (5,8%);*
ZFYVE26 (5,3%); *ATL1 (4,3%);* *CYP7B1 (3,8%);*
CAPN1 (2,9%); *KIF5A (2,9%);* *SACS (2,9%);*
ARG1 (1,4%); *ATP13A2 (1,4%);* *B4GALNT1 (1%);*
BSCL2 (1%); *CYP27A1 (1%);* *KCNA2 (1%);*
KIF1A (1%); *REEP1 (1%);* *REEP2 (1%);*
RNASEH2B (1%); *ABCD1 (0,5%);* *ALS2 (0,5%);*
CYP2U1 (0,5%); *DDHD1 (0,5%);* *FA2H (0,5%);*

Highlights

Identification of variants in **genes causing overlapping phenotypes** in patients with an apparent pure spastic paraplegia phenotype

Case #1

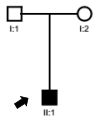
1 year-old male with pure spastic paraplegia. Normal brain MRI. Spastic hypertonia of the lower limbs.



homozygous variant in *ALS2*
NM_020919.3:c.[4261C>T];[c.4261C>T] // p.(Arg1421*)

Case #2

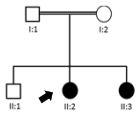
58 years-old male with spastic paraplegia



homozygous variant in *GALC*
NM_000153.3:c.[927A>C];[927A>C] // p.(Leu309Phe)

Case #3

9 years-old female with spastic paraglegia. Polyneuropathy.



homozygous variant in SYNE1
NM_182961.3(SYNE1):c.[21401del];[21401del] // p.(Ser7134Ilefs*9)

Conclusions

This work:

1. Contributed to the molecular, clinical and genetic heterogeneity of HSPs.

2. Demonstrates the importance of testing genes defective in other differential diagnosis, with overlapping clinical features (such as *SACS*, *ARG1* and *KCNA2*) – strong implications in NGS panels design.

3. Depicted a high number of patients with VUS and/or single heterozygous variants in genes associated to diseases with an autosomal recessive inheritance - besides the importance of identifying a missing pathogenic allele, highlighted :
   - the difficulty of interpretating VUS;
   - the importance of functional studies to clarify their causative role and, ultimately, provide a definitive diagnosis of HSP;
   - the possibility of finding, among these variants/*locus*, further modes of genetic inheritance, even of oligogenic nature.

4. The number of patients without variants reported (n=135) might indicate that a large number of HSPs causing genes and probably novel pathogenic mechanisms leading to the disease are yet to be discovered.