Next Generation gene testing telling a story

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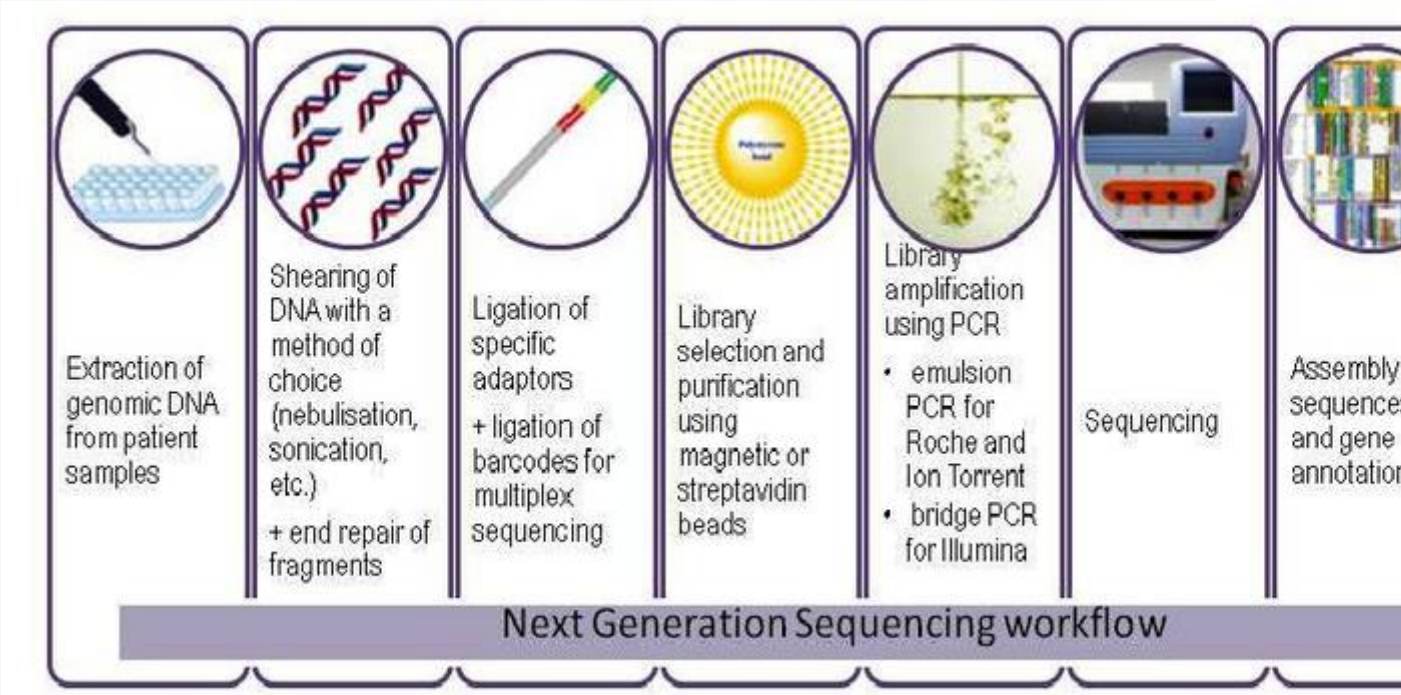
Much of HSP genetics still not understood

It was widely thought that the breakthrough technology of next generation gene testing would unlock the mystery surrounding HSP genetics. Now, less than a decade on, less than half of all genetic tests where HSP is suspected, deliver a positive result where the genetic culprit is specifically identified. This is despite modern HSP gene testing panels covering almost 100 gene locations – 30 times more powerful than the testing available a decade ago.



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This large study of 193 Portuguese HSP families from the 1990s had 98 unsolved cases. Next-generation sequencing was used successfully to identify the responsible gene in 20 of these 98. This still leaves fully 40% of cases unsolved despite the enormous increase in power available with gene testing nowadays. The authors of this study conclude that there is still a large set of unknown genes responsible for HSP, likely with disease-causing mechanisms not yet discovered or even modes of inheritance that are not yet known.

Abstract

Hereditary spastic paraplegias (HSP) are neurodegenerative disorders characterized by lower limb spasticity and weakness that can be complicated by other neurological or non-neurological signs.

Despite a high genetic heterogeneity (>60 causative genes), 40-70% of the families remain without a molecular diagnosis. Analysis of one of the pioneer cohorts of 193 HSP families generated in the early 1990s in Portugal highlighted that SPAST and SPG11 are the most frequent diagnoses.

We have now explored 98 unsolved families from this series using custom next generation sequencing panels analyzing up to 70 candidate HSP genes. We identified the likely disease-causing variant in 20 of the 98 families with KIF5A being the most frequently mutated gene. We also found 52 variants of unknown significance (VUS) in 38% of the cases. These new diagnoses resulted in 42% of solved cases in the full Portuguese cohort (81/193). Segregation of the variants was not always compatible with the presumed inheritance, indicating that the analysis of all HSP genes regardless of the inheritance mode can help to explain some cases.

Our results show that there is still a large set of unknown genes responsible for HSP and most likely novel mechanisms or inheritance modes leading to the disease to be uncovered, but this will require international collaborative efforts, particularly for the analysis of VUS.

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Massive sequencing of 70 genes reveals a myriad of missing genes or mechanisms to be uncovered in hereditary spastic paraplegias.

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