Hereditary spastic paraplegias (HSP) are one of the most heterogeneous neurological disorders. All modes of inheritance have been described for the 67 known causative genes implicated up to now. Recent advances in molecular genetics have revealed clinico-genetic heterogeneity of these disorders including their clinical and genetic overlap with other diseases of the nervous system. The systematic analysis of a large set of genes, including exome sequencing, is unmasking unusual phenotypes or inheritance modes associated with mutations in HSP genes and related genes involved in various neurological diseases. A new nosology may emerge after integration and understanding of these new data to replace the current classification. Collectively, functions of the known genes implicate the disturbance of intracellular membrane dynamics and trafficking as the consequence of alterations of cytoskeletal dynamics, lipid metabolism and organelle structures, which represent in fact a relatively small number of cellular processes that could help to find common curative approaches, which are still lacking.