Translational Neurogenetics towards the identification of targets for the development of therapeutic strategies

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Identification of the mutations that are associated with specific genetic diseases has been the aim of many studies since the characterisation of the DNA molecule, hoping for possible treatment after the causative mutation has been identified. The great majority of monogenenic disease genes has thus far been identified, however, despite major advances in the development of various technologies, gene therapy has yet to become a tangible therapeutic approach. The pathogenetic mechanisms have to be elucidated in order to facilitate possible therapeutic protocols, not necessarily targeting the genetic defect as such, but probably other molecules along the deficient pathway.

It has become apparent that neurogenetic diseases such as the ataxias, spastic paraplegias and neuropathies are characterised by vast genetic heterogeneity. Many families remain undiagnosed at the molecular genetic level despite extensive analysis of currently known genes. It is suspected that these remaining families could each harbour a novel disease gene mutation, thus further increasing the genetic heterogeneity of these rare diseases. Currently, next generation sequencing (NGS) facilitates robust identification of the disease causing mutation in familial and sporadic cases within a considerably reduced discovery time. Indeed, the past couple of years have proven these expectations to be realistic with an increasing number of rare and ultra-rare disease genes being identified. This advantage is giving the opportunity to scientists to focus on the functional characterisation of mutations at various levels, in silico, in vitro and in vivo, thus driving innovation towards identification of targets for the development of therapeutic strategies. Functional characterisation of rare disease mutations is going to provide the missing links within the pathogenetic mechanisms and pathways of specific phenotypes. Thus, innovative approaches towards identification of possible therapeutic targets, are currently focusing on rare diseases. Precision medicine is becoming a realistic scenario.