

Genetic Analysis of Inherited Leukodystrophies: Genotype-Phenotype Correlations in the CSF1R Gene.

Houlden, H, MD MRCP PhD.

6th floor DNA laboratory, Institute of Neurology, Queen Square, London WC1N 3BG. Email: h.houlden@ucl.ac.uk

Research question and background

Objective: To better understand the genetic role of mutations in this gene, we sequenced a large cohort of adult onset leukodystrophy cases with a clinical or neuropathological diagnosis. These cases were collected from around the world from clinical series and brain banks including the Netherlands Brain Bank.

The leukodystrophies comprise a clinically and genetically heterogeneous group of progressive hereditary neurological disorders mainly affecting the myelin in the central nervous system. Their onset is variable from childhood to adulthood and presentation can be with a variety of clinical features that include mainly for adult-onset cases cognitive decline, seizures, parkinsonism, muscle weakness, neuropathy, spastic paraplegia, personality/behavioral problems, and dystonia. Recently, Rademakers and colleagues identified mutations in the CSF1R gene as the cause of hereditary diffuse leukoencephalopathy with spheroids (HDLS), offering the possibility for an in-life diagnosis. The detection of mutations in this gene in cases diagnosed with different clinical entities further demonstrated the difficulties in the clinical diagnosis of HDLS.

Design: Whole-exome sequencing and follow upscreening by Sanger sequencing.

Main Outcomes and Measures:

Mutations in CSF1R. Results: We identified 12 probands with mutations in CSF1R. The clinical diagnoses given to these patients included dementia with spastic paraplegia, corticobasal degeneration syndrome, and stroke disorders. Our study shows that CSF1R mutations are responsible for a significant proportion of clinically and pathologically proven HDLS.

Results and conclusion

These results give an indication of the frequency of CSF1R mutations in a European leukodystrophy series and expand the phenotypic spectrum of disorders that should be screened for this gene.