Am J Med Genet C Semin Med Genet. 2020 Dec;184(4):876-884. doi: 10.1002/ajmg.c.31848. Epub 2020 Oct 20.

The odyssey of complex neurogenetic disorders: From undetermined to positive

Valeria Salinas [1 2], Patricia Vega [1], Luca Marsili [3], Josefina Pérez-Maturo [1 2], Nerina Martínez [1], Lucia Zavala [1], Dolores González-Morón [1], Nancy Medina [1], Sergio A Rodriguez-Quiroga [1], Hernán Amartino [4], Clarisa Maxit [5], Andrea Sturchio [3], Barbara Grimberg [3], Kevin Duque [3], Betiana Comas [6], Walter Silva [5], Damián Consalvo [7], Ignacio Sfaello [8], Alberto J Espay [3], Marcelo A Kauffman [1 2]

Affiliations

PMID: 33084218 DOI: 10.1002/ajmg.c.31848

Abstract

The genetic and phenotypic heterogeneity of neurogenetic diseases forces patients and their families into a "diagnostic odyssey." An increase in the variability of genetic disorders and the corresponding gene-disease associations suggest the need to periodically re-evaluate the significance of variants of undetermined pathogenicity. Here, we report the diagnostic and clinical utility of Targeted Gene Panel Sequencing (TGPS) and Whole Exome Sequencing (WES) in 341 patients with suspected neurogenetic disorders from centers in Buenos Aires and Cincinnati over the last 4 years, focusing on the usefulness of reinterpreting variants previously classified as of uncertain significance. After a mean of ±2years (IC 95:0.73-3.27), approximately 30% of the variants of uncertain significance were reclassified as pathogenic. The use of next generation sequencing methods has facilitated the identification of both germline and mosaic pathogenic variants, expanding the diagnostic yield. These results demonstrate the high clinical impact of periodic reanalysis of undetermined variants in clinical neurology.

Keywords: diagnostic odyssey; mosaicism; targeted gene panel sequencing; variants of unknown significance; whole exome sequencing.

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