

Updates from the International NF-SWN Genes Variant Curation Expert Panel (VCEP) to Improve Genetic Testing of Neurofibromatosis and Schwannomatosis

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BACKGROUND

Neurofibromatosis type 1 (NF1); *NF2*-, *SMARCB1*-, and *LZTR1*-related schwannomatosis (SWN); and Legius syndrome (LGSS) require a genetic diagnosis (1) to confirm clinical suspicion in patients with indeterminate phenotype, (2) to better understand a patient’s prognosis and (3) for family planning. Variant interpretation and classification of the five genes causing these disorders (*NF1*, *NF2*, *SMARCB1*, *LZTR1*, and *SPRED1*) is challenging due to the broad mutational spectrum, the paucity of clear mutational “hotspots”, and the high proportion of non-coding and splicing variants. Many of the patients do not have a family history due to high *de novo* and mosaicism rate and/or variable penetrance and expressivity and do not meet diagnostic criteria in the early stages of these disorders. These patients would benefit from an accurate genetic test for clinical use and follow-up.

METHODS

Thirty-seven individuals from North and South America, Australia, and Europe with expertise in NF1, LGSS, and SWN (or other related hereditary tumor predisposition pathologies) or from high-volume diagnostic laboratories (academic and commercial) volunteered to develop ACMG/AMP variant interpretation rules specific for NF-SWN genes as members of a Variant Curation Expert Panel (VCEP) in the framework of the NIH-funded ClinGen Hereditary Cancer Clinical Domain Working Group. This panel of experts includes clinical and molecular geneticists, variant scientists, genetic counselors, epidemiologists, neurosurgeons, and others who regularly participate in the diagnosis and/or clinical management of this group of disorders.

ACMG STANDARDS AND GUIDELINES

Genetics of Medicine

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

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