NIPBL

NIPBL (NIPBL Cohesin Loading Factor) is a Protein Coding gene. Diseases associated with NIPBL include Cornelia De Lange Syndrome 1 and Cornelia De Lange Syndrome. Among its related pathways are Mitotic Telophase/Cytokinesis and Cell Cycle, Mitotic. Gene Ontology (GO) annotations related to this gene include chromatin binding and protein C-terminus binding.

Post-zygotically acquired genetic variants, or somatic variants, that arise during cortical development have emerged as important causes of focal epilepsy, particularly those due to malformations of cortical development. Pathogenic somatic variants have been identified in many genes within the PI3K-AKT-mTOR-signaling pathway in individuals with hemimegalencephaly and focal cortical dysplasia (type II), and more recently in SLC35A2 in individuals with focal cortical dysplasia (type I) or non-dysplastic epileptic cortex. Given the expanding role of somatic variants across different brain malformations, Lai et al. sought to delineate the landscape of somatic variants in a large cohort of patients who underwent epilepsy surgery with hemimegalencephaly or focal cortical dysplasia. They evaluated samples from 123 children with hemimegalencephaly (n=16), focal cortical dysplasia type I and related phenotypes (n=48), focal cortical dysplasia type II (n=44), or focal cortical dysplasia type III (n=15). They performed high-depth exome sequencing in brain tissue-derived DNA from each case and identified somatic single nucleotide, indel, and large copy number variants. In 75% of individuals with hemimegalencephaly and 29% with focal cortical dysplasia type II, they identified pathogenic variants in PI3K-AKT-mTOR pathway genes. Four of 48 cases with focal cortical dysplasia type I (8%) had a likely pathogenic variant in SLC35A2. While no other gene had multiple disease-causing somatic variants across the focal cortical dysplasia type I cohort, four individuals in this group had a single pathogenic or likely pathogenic somatic variant in CASK, KRAS, NF1, and NIPBL, genes associated with neurodevelopmental disorders. No rare pathogenic or likely pathogenic somatic variants in any neurological disease genes like those identified in the focal cortical dysplasia type I cohort were found in 63 neurologically normal controls (P = 0.017), suggesting a role for these novel variants. They also identified a somatic loss-of-function variant in the known epilepsy gene, PCDH19, present in a small number of alleles in the dysplastic tissue from a female patient with focal cortical dysplasia IIIa with hippocampal sclerosis. In contrast to focal cortical dysplasia type II, neither focal cortical dysplasia type I nor III had somatic variants in genes that converge on a unifying biological pathway, suggesting greater genetic heterogeneity compared to type II. Importantly, they demonstrate that FCD types I, II, and III, are associated with somatic gene variants across a broad range of genes, many associated with epilepsy in clinical syndromes caused by germline variants, as well as including some not previously associated with radiographically evident cortical brain malformations [1].

1)
Lai D, Gade M, Yang E, Koh HY, Lu J, Walley NM, Buckley AF, Sands TT, Akman CI, Mikati MA, McKhann GM, Goldman JE, Canoll P, Alexander AL, Park KL, Von Allmen GK, Rodziyevska O, Bhattacharjee MB, Lidov HGW, Vogel H, Grant GA, Porter BE, Poduri AH, Crino PB, Heinzen EL. Somatic variants in diverse genes leads to a spectrum of focal cortical malformations. Brain. 2022 Apr 20:awac117. doi: 10.1093/brain/awac117. Epub ahead of print. PMID: 35441233.