Neurodevelopmental diseases (NDDs) are a common cause of disability. The diseases may affect the brain globally or only in specific regions. Individuals with some of the most common NDDs, such as attention hyperactivity disorder and autism spectrum disorders, may show significant cognitive or behavioral changes without major structural abnormalities (Morris-Rosendahl and Crocq, 2020). At the other end of the spectrum lies pontocerebellar hypoplasia (PCH), a disorder of prenatal onset affecting mainly, but not exclusively, the cerebellum and pons. Genetic dissection of this phenotype has now led to the identification of recessive mutations in a number of genes, most commonly involved in exosome function, tRNA charging and splicing, and other RNA functions, but PCH can also be seen with mutations in genes not commonly associated with these conditions such as RELN or VLDLR (reviewed in van Dijk et al., 2018).

In this issue of Neuron, Chai et al. (2021) analyze several families with neurodegeneration and marked pontocerebellar hypoplasia and microcephaly and identify recessive (bi-allelic) mutations in peptidyl-prolyl isomerase-like 1 (PPIL1) and pre-RNA-processing-17 (PRP17). PPIL1 patient mutation knockin mice develop neuronal apoptosis. Loss of either protein affects splicing predominantly involving GC-rich and short introns. With eight individuals were identified. These additional pedigrees contributed different mutations including a six amino acid insertion as well as compound heterozygosity of mutations.

All individuals exhibited PCH with microcephaly. Chai et al. (2021) defined this presentation as a unique clinical entity versus 11 previously described PCH subtypes (van Dijk et al., 2018), which they designated PCHM (PCH+Microcephaly). The phenotype, however, encompasses additional features, including seizures, as well as delayed motor and language development. Attesting to a more global involvement of the central nervous system (CNS), brain imaging showed cortical changes with gyral simplification in most affected individuals in addition to posterior fossa changes. Although microcephaly is part of other PCH phenotypes, for example, PCH2, microcephaly due to PPIL1 mutations is universal, congenital, and severe. In contrast to some forms of PCH, PCHM not only is a developmental hypoplasia but also shows clear postnatal progression (van Dijk et al., 2018). In general, clinical severity correlated with the degree of impairment of protein stability or function.

PPIL1 is a cyclophilin family protein characterized by peptidylprolyl isomerase (PPIase) activity and a spliceosomal complex protein that interacts with the pre-mRNA splicing factors pre-RNA-processing-17 (PRP17), SKIP, and RBM22. PPIL1 also functions as a chaperone of protein folding and can interact with the HIV-1 capsid facilitating virion formation. PPIL1 and other cyclophilins directly interact with the immunosuppressive drug cyclosporin A, which can block HIV-1 capsid interaction as well as its isomerase activity. A main role for PPIL1 described by Chai et al. (2021) is its interaction with SKIP, which is required for spliceosome activation. Indeed, all PPIL1 patient mutations affected either its own stability or its interaction with SKIP. When overexpressed in cultured cells, reduced protein stability for the variant forms of PPIL1 or PRP17 and propensity for aggregation for the T107A and R131Q PPIL1 variants were observed. Chai et al. (2021) also examined the effect of PPIL1 mutations on SKIP interaction. The SKIP binding site is in a non-enzymatic region of PPIL1. Yet PPIL1 variants (T107A and R131Q) located in the enzymatic region failed to associate with SKIP. Thus, mutations in PPIL1 and PRP17 affect protein stability, and PPIL1 mutations alter interaction with SKIP.

Given the interactions of PPIL1 with other proteins, Chai et al. (2021) also looked for mutations in PRP17, SKIP, and RBM22 in their pedigree database. They identified one multiplex consanguineous family with affected individuals homozygous for a PRP17 F502C missense mutation. Isomerization of PRP17 mediated by PPIL1 was not critical for functions in splicing and neuronal survival.

Chai et al. (2021) next examined the consequences of PCH mutations in splicingosome function, neuronal survival, and neurodegeneration. They identified numerous significant differential splicing events (SDSEs) in PPIL1 knockout HAP1 cells. These included skipped exons, mutually exclusive exons, a selection of alternative 5’ and 3’ splice sites, and retained introns. Functional inactivation of PPIL1 predominantly impacted the splicing of short and high GC-content introns. Further experiments in mice...
homozygous for the A99T mutation in PPIL1 that abrogates SKIP binding also showed numerous splicing alterations in critical brain pathways. Splicing changes were not uniform but impacted predominantly splicing of short and high GC-content introns. The most significant splicing changes occurred in short introns that had a GC content > 70%. These mice also had microcephaly with reduced neuronal counts. Supporting the presence of neurodegeneration, they observed upregulation of cleaved caspase-3 and p53 expression at different embryonic developmental stages, predominantly localized at the cortical plate.

The question remained why mutations in PPIL1 and PRP17 cause brain-specific PCHM while cell death in other organs was not observed. Chai et al. (2021) speculate that neuronal genes have a higher susceptibility to global splicing defects and invoke the possibility that neurons may be more susceptible in the developing brain when alternatively spliced genes tend to be longer. Thus, postmitotic neurons might accumulate higher levels of misspliced mRNA, affecting protein production or accumulating toxic or unfolded proteins.

Other neurodegenerative diseases are characterized by splicing defects. Mutations in splicing factors such as Fused in Sarcoma (FUS) and TAR DNA-binding protein 43 (TDP-43) are recognized as being involved in neurodegeneration, especially in motor neuron death and neurodegenerative diseases. Muta-
tions in MSC genes had been previously localized at the cortical plate. In summary, the study by Chai et al. (2021) provides novel insights into the function of major spliceosome complex (MSC) genes in PCHM. Although mutations in MSC genes had been previously linked to cancers and autosomal-dominant retinitis pigmentosa (Nik and Bowman, 2019), this study links mutations in MSC genes to neurodevelopmental defects and changes in splicing that affect a subset of mRNAs. Neurons appear to be particularly sensitive to these splicing defects, leading to apoptotic neurodegeneration.

REFERENCES


