IN THIS ISSUE

Variants in major phosphatase yield broad neurodevelopmental phenotypes

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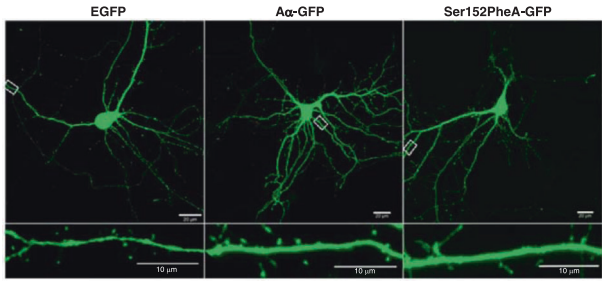

Protein phosphatase 2A (PP2A) is a central serine/threonine phosphatase. Variants in the genes that encode PP2A's catalytic C and regulatory B-type subunits are often associated with neurodevelopmental disorders (NDDs), but few have been found in *PPP2R1A*, the gene encoding the scaffolding A subunit. In this issue, Lenaerts and colleagues report the discovery of 12 novel de novo variants in *PPP2R1A* in individuals with a wide range of NDDs. The researchers identified the 12 novel and 4 previously reported de novo variants in 30 individuals with NDD. Nearly all individuals displayed developmental delay that indicated mild to severe intellectual disability (ID). The only exception was an individual with autism spectrum disorder and low average IQ. Some individuals also displayed brain malformations such as corpus callosum hypoplasia, macro- or microcephaly, and epilepsy. Uniform traits across the group included neurodevelopmental delay, prolonged hypotonia, and language delay. When the researchers correlated clinical findings with the identified variants, patterns emerged. For example, individuals harboring p.Met180Thr and p.Met180Val typically showed moderate ID, whereas those with p.Arg182Trp showed severe ID. Binding assays revealed that variants generally reduced binding to regulatory B-type subunits, but to varying extents. Eight variants also showed decreased binding to the catalytic C subunit, five of which reduced PP2A activity by as much as 70%. Only one variant, p.Ser152Phe, did not exhibit functional impairment. When the researchers overexpressed the protein in mature primary hippocampal neurons, they saw significantly lower dendritic spine numbers compared with wild-type expressing neurons, suggesting that the variant may be pathogenic and play a role in regulating dendritic spine number. The authors conclude that *PPP2R1A* variants lead to a wide phenotypic spectrum and biochemical dysfunction with implications for diagnosis, clinical management, and follow-up of patients. —*V. L. Dengler, News Editor*

X-linked encephalopathy shows uneven phenotypic patterns

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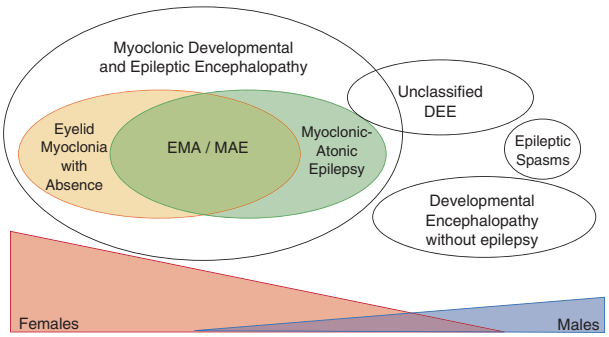

The X-linked gene neurite extension and migration factor (*NEXMIF*) is critical to normal brain function with likely roles in neuronal morphogenesis, migration, and synapse formation. Pathogenic variants in *NEXMIF* were first identified in males with intellectual disability (ID), subtle dysmorphic features, and occasionally epilepsy. Females typically had generalized epilepsy and less serious ID, suggesting a role for X chromosome inactivation (XCI). Stamberger and colleagues delineate the phenotypic spectrum of *NEXMIF* encephalopathy and examine phenotype–genotype correlations in males and females. The researchers recruited a cohort of nearly 90 individuals with *NEXIMF* encephalopathy and conducted a series of phenotypic, genetic, and neurological analyses. All 24 males in the study exhibited developmental delay, with most showing severe to profound ID. In contrast, most females in the study had mild to moderate ID and, overall, displayed a more variable phenotype than males. Although the vast majority of patients (83%) presented with seizures, epilepsy was more common in females than males. The researchers also observed dysmorphic features in nearly half of patients, but automated facial analysis could not distinguish patients from unaffected controls. Seven of 32 females showed a skewed XCI pattern; however, the researchers did not find a correlation between phenotype and XCI. Genotyping revealed 58 unique *NEXMIF* variants among the cohort, including 30 novel variants. Nearly all variants were de novo, but 13% were maternally inherited. All variants, which included stop gain, frameshift, and large structural variants, were predicted to decrease protein expression. The authors conclude that *NEXMIF* encephalopathy is an X-linked disorder caused by de novo or maternally inherited loss-of-function variants, in which females show a broader phenotypic pattern and males are more severely affected. —*V. L. Dengler, News Editor*