PCDH19-related epilepsy

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Objective:

To characterize the features associated with PCDH19-related epilepsy, also known as "female-limited epilepsy."

Methods:

We analyzed data from participants enrolled in the PCDH19 Registry, focusing on the seizure-related, developmental, neurobehavioral, and sleep-related features. We evaluated variants for pathogenicity based on previous reports, population databases, and in silico predictions, and included individuals with pathogenic or potentially pathogenic variants. We performed a retrospective analysis of medical records and administered a targeted questionnaire to characterize current or past features in probands and genotype-positive family members.

Results:

We included 38 individuals with pathogenic or potentially pathogenic variants in PCDH19: 21 de novo, 5 maternally inherited, 7 paternally inherited, and 5 unknown. All 38 had epilepsy; seizure burden varied, but typical features of clustering of seizures and association with fever were present. Thirty individuals had intellectual disability (ID), with a wide range of severity reported; notably, 8/38 (22%) had average intellect. Behavioral and sleep dysregulation were prominent, in 29/38 (76%) and 20/38 (53%), respectively. Autistic features were present in 22/38 (58%), of whom 12 had a formal diagnosis of autism spectrum disorder. We had additional data from 5 genotype-positive mothers, all with average intellect and 3 with epilepsy, and from 1 genotype-positive father.

Significance:

Our series represents a robust cohort with carefully curated PCDH19 variants. We observed

seizures as a core feature with a range of seizure types and severity. Whereas the majority of individuals had ID, we highlight the possibility of average intellect in the setting of PCDH19-related epilepsy. We also note the high prevalence and severity of neurobehavioral phenotypes associated with likely pathogenic variants in PCDH19. Sleep dysregulation was also a major area of concern. Our data emphasize the importance of appropriate referrals for formal neuropsychological evaluations as well as the need for formal prospective studies to characterize the PCDH19-related neurodevelopmental syndrome in children and their genotype-positive parents.