What is PCDH19?

The PCDH19 (protocadherin-19) gene provides instructions for making protocadherin, a protein involved in cell-to-cell adhesion and signaling between neurons. Pathogenic variants in PCDH19 are related to epilepsy and a spectrum of neurodevelopmental symptoms. The PCDH19 gene is located on the X chromosome. Typically, females have two X chromosomes while males have an X and a Y chromosome. In general, X-linked disorders tend to affect males more severely. In females, X-linked disorders tend to be asymptomatic or mildly symptomatic.

Interestingly, PCDH19-related epilepsy follows a unique X-linked pattern of inheritance in which females with two X chromosomes show the core features of the disease while males with one X chromosome are largely unaffected. This is likely due to a process known as cellular interference. Cellular interference is caused when two different cell populations are created through X-inactivation in females. During X-inactivation, one copy of the X-chromosome, including one copy of the PCDH19 gene, is randomly silenced in each cell. Males who only have one X chromosome are symptomatic when a pathogenic PCDH19 variant arises later during embryonic development. This process, known as post-zygotic mutation or somatic mosaicism, creates a similar scenario in which two cell populations exist.

Many different types of DNA variants have been identified throughout the PCDH19 gene. However, the variant type is not necessarily indicative of symptom severity. Individuals with the same variant, even within the same family, may have different symptoms. This could be due to variable patterns of X-chromosome inactivation, genetic modifiers, or other factors yet to be fully understood.

Pathogenic PCDH19 variants may be inherited from a parent or arise spontaneously for the first time in a child (*de novo*). If inherited from a parent, the parent may or may not have a personal history of symptoms. There may not be a family history of seizures, learning or developmental challenges in the family, particularly if the variant arose *de novo*.

What types of seizures (and epilepsies) are associated with variants in PCDH19?

Many individuals with PCDH19-related epilepsy develop seizures within the first 3 years of life. The first seizure(s) are often in the setting of a febrile illness. For some, the initial presentation can be dramatic with seizure clusters (numerous seizures in short period of time), often difficult to control, and may be misdiagnosed as encephalitis. Over time, seizures and seizure cluster occurrences can become unprovoked. Most individuals have focal or multifocal seizures, but apparent generalized tonic-clonic seizures have also been reported. Non-motor focal seizures with impaired awareness and focal tonic seizures with

impaired awareness are the predominant seizure types. They can be associated with autonomic changes. Seizures described as generalized tonic-clonic often begin as focal, followed by rapid generalization. Occurrence in clusters is characteristic for seizures with PCDH19-related epilepsy. The types of clusters are variable and can be as frequent as several seizures per hour over several hours or days, or several seizures per day over several days, often with intervening long periods of seizure freedom which can last up to several months. Seizures are theoretically life-long but there are some data suggesting that a subset of individuals might have significant improvement or even seizure freedom after puberty.

What non-seizure symptoms may be seen with PCDH19 variants?

Neurodevelopmental involvement, including developmental delay, intellectual disability, learning disability, autism spectrum disorder, and behavioral dysregulation are common. Neuropsychiatric manifestations are also common and include symptoms related to anxiety such as obsessive-compulsive behaviors, or mood abnormalities. Sleep dysregulation is also prevalent. Affected individuals may have some or all these features, each with varying severity. Schizophrenia has been reported in a small percentage of adult females, many of whom had prior neuropsychiatric symptoms. Some individuals with PCDH19-related epilepsy have none of these additional features.

How are PCDH19 variants diagnosed?

PCDH19 variants are identified through genetic testing. Targeted testing of the PCDH19 gene may be performed if a high likelihood of this diagnosis is suspected. Multi-gene panels and exome sequencing may also be used to identify PCDH19 variants. In the future, other testing options may become available.

Genetic counseling prior to genetic testing is an important step in making sure that the best testing strategy is selected, and that patients and families understand the risks, benefits, limitations, and outcomes of testing.

How is PCDH19-related epilepsy treated?

To date, there are no approved targeted therapies for PCDH19-related epilepsy, although clinical trials are underway. Currently, anti-seizure medications or other treatment options are recommended based on seizure type. Clusters can be difficult to treat, so providers may need to tailor the status epilepticus treatment plan (e.g., immediate administration of rescue medication as opposed to waiting for 5 minutes or for a second seizure, or consideration of a steroid bolus). A written, detailed seizure action plan for home and hospital use can be very

helpful. This plan might need to be tailored for each individual depending on prior response and cluster progression. In terms of daily anti-seizure medications, while there are retrospective reports indicating some medications are more effective than others (e.g., clobazam), no formal, randomized controlled trials of classical anti-seizure medications have been done in this population. Ganaxolone, an oral neurosteroid, is currently in clinical trial phases awaiting formal efficacy results.

Support services may be needed for learning, development, behavior, and mental health. Children should receive formal evaluations by a developmental specialist or neuropsychologist if developmental concerns are present or develop over time. An Individual Education Plan (IEP) should be in place in coordination with the school and developmental specialists, if needed. Applied Behavior Analysis (ABA) therapy should be made available as recommended for individuals with autism spectrum disorder. Evaluation by a sleep specialist may also be beneficial if a sleep disorder or sleep challenges are present.

How common is PCDH19-related epilepsy?

We currently do not have enough data to say, with certainty, how common PCDH19-related epilepsy may be. Hundreds of cases have been reported in the literature, but many individuals have been diagnosed that are not reported.

What is the outlook for PCDH19-related epilepsy?

The outlook for PCDH19-related epilepsy is variable and is dependent upon the symptoms with which each individual presents. Seizures are often reported to decrease after puberty in females, but there are no data to suggest whether medication discontinuation is safe. Neurodevelopmental and neuropsychiatric outcomes are variable, and might worsen, stabilize, or improve over time.

For more information

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