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FULL-LENGTH ORIGINAL RESEARCH

Schizophrenia is a later-onset feature of *PCDH19* Girls Clustering Epilepsy

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Summary

Objective: To investigate the occurrence of psychosis and serious behavioral problems in females with protocadherin 19 gene (*PCDH19*) pathogenic variants.

Methods: We evaluated whether psychosis and serious behavioral problems had occurred in 60 females (age 2-75 years) with *PCDH19* pathogenic variants belonging to 35 families. Patients were identified from epilepsy genetics databases in Australia, New Zealand, the United States, and Canada. Neurologic and psychiatric disorders were diagnosed using standard methods.

Results: Eight of 60 females (13%) from 7 families developed a psychotic disorder: schizophrenia (6), schizoaffective disorder (1), or an unspecified psychotic disorder (1). Median age at onset of psychotic symptoms was 21 years (range 11-28 years). In our cohort of 39 females aged 11 years or older, 8 (21%) developed a psychotic disorder. Seven had ongoing seizures at onset of psychosis, with 2 continuing to have seizures when psychosis recurred. Psychotic disorders occurred in the setting of mild (4), moderate (2), or severe (1) intellectual disability, or normal intellect (1). Preexisting behavioral problems occurred in 4 patients, and autism spectrum disorder in 3. Two additional females (3%) had psychotic features with other conditions: an adolescent had recurrent episodes of postictal psychosis, and a 75-year-old

Scheffer and Andrade contributed equally

woman had major depression with psychotic features. A further 3 adolescents (5%) with moderate to severe intellectual disability had onset of severe behavioral disturbance, or significant worsening.

Significance: We identify that psychotic disorders, including schizophrenia, are a later-onset manifestation of *PCDH19* Girls Clustering Epilepsy. Affected girls and women should be carefully monitored for later-onset psychiatric disorders.

KEY WORDS

epilepsy, psychiatry, psychosis, psychotic disorders, seizures

1 | INTRODUCTION

Protocadherin 19 gene (*PCDH19*) pathogenic variants (Online Mendelian Inheritance in Man [OMIM] 300460) were initially identified in a family with Epilepsy and Mental Retardation limited to Females (EFMR, OMIM 300088).^{1,2} However, given that about one-fourth of women do not have mental retardation,^{1,3} the new name of Girls Clustering Epilepsy (GCE) was suggested to aid recognition of this distinctive disorder with an unusual inheritance pattern.⁴ *PCDH19*-GCE occurs in heterozygous females, whereas males are usually unaffected transmitting carriers. Rare males with mosaic pathogenic variants are affected, reflecting the female pattern of 2 X chromosomes and the consequent coexistence of cells with and without mutant *PCDH19*.^{2,5,6} Girls with *PCDH19* pathogenic variants present with recurrent clusters of seizures triggered by fever in infancy or early childhood. Intellectual can range from normal to severe intellectual disability (ID).^{1,2,7}

Although psychiatric features were noted in a few females reported in the original studies of *PCDH19*-GCE (called EFMR in these studies),^{1,8,9} behavioral and psychiatric comorbidities are common and may pose the most disabling problem in adulthood.³ An array of psychiatric comorbidities has been described including severe behavioral problems, obsessive features, and autism spectrum disorder (ASD). In adult life, we previously reported 2 women with a schizophreniform psychosis,¹ and an additional woman with psychosis has been subsequently reported.¹⁰

We hypothesized that psychosis was a later-onset feature of *PCDH19*-GCE. We therefore analyzed the presence of psychosis and serious behavioral problems in a cohort of females with *PCDH19* pathogenic variants.

2 | METHODS

2.1 | Study cohort

Patients were ascertained from the epilepsy genetics databases of the authors located in Australia and New Zealand,

Key Points

- *PCDH19* Girls Clustering Epilepsy (GCE) causes a distinctive phenotype of early onset clusters of seizures often triggered by fever
- We identified psychotic disorders as a later-onset feature of *PCDH19*-GCE in 8 females with median onset at 21 years (range 11-28 years)
- We found that 21% of females with *PCDH19*-GCE who were aged 11 years or older, developed psychotic disorders, including schizophrenia in 15%

the United States, and Canada. These databases include all patients presenting with genetic epilepsy and their relatives who consent to research participation. The database includes information on pathogenic variants. Families A, B, E, and G were published previously^{1,2,11,12}; however, their psychiatric phenotype has been evaluated in detail for this study. We analyzed the frequency of psychosis in adolescent and adult women with a *PCDH19* pathogenic variant, using the youngest age at onset of psychosis observed in our cohort to delineate the group of interest.

2.2 | Phenotyping

We use the term “*PCDH19*-Girls Clustering Epilepsy” (or *PCDH19*-GCE) for the well-recognized epilepsy syndrome associated with *PCDH19* pathogenic variants, as suggested previously.^{4,13,14} We examined whether each female had experienced psychosis and serious behavioral problems and the evolution of these symptoms over time. We also evaluated the epilepsy phenotype, developmental course and intellect, magnetic resonance imaging (MRI) findings, genetic results, and the family history. Information was obtained using a validated seizure questionnaire,¹⁵ clinical interviews, and review of medical records. Psychotic disorders were diagnosed using the Diagnostic and Statistical

Manual of Mental Disorders, 5th Edition (DSM-5) by an academic psychiatrist (A.S.B.), after local assessment by a psychiatrist at the time of the patient's presentation.¹⁶ The level of intellectual disability was based on intelligence quotient (IQ) scores obtained through formal psychometric assessment. Seizure types and epilepsy syndromes were classified according to the 2017 International League Against Epilepsy (ILAE) Classification of the Epilepsies.^{17,18}

2.3 | Genotyping

PCDH19 is a highly conserved gene as illustrated by its intolerance to variation (Residual Variation Intolerance Score [RVIS] = -0.89) and to loss of function variation (probability of intolerance to loss of function [pLI] score = 1.00).¹⁹ In the research genetic epilepsy database, only pathogenic variants were included, based on the criteria of the American College of Medical Genetics.¹⁹ We present the data on pathogenic variants identified in females with a psychotic disorder in Table S1. *PCDH19* pathogenic variants or deletions were reported in accordance with its longest isoform 1 (NM_001184880.1).

2.4 | Ethical statement

Patients, or their parents or legal guardians in the setting of minors or those with intellectual disability, gave written informed consent for inclusion in our study. This study was approved by the local institutional human research

ethics committee (Austin Health reference H2007/02961), the Health and Disability Ethics Committee (New Zealand), and the Research Ethics Board (Toronto Western Hospital 15-9512).

3 | RESULTS

We studied 60 females with *PCDH19* pathogenic variants from 35 families. Females were aged between 2 and 75 years (median age 18 years).

3.1 | *PCDH19* Girls Clustering Epilepsy with chronic psychotic disorders (n = 8)

Eight of our cohort of 60 females developed a psychotic disorder. Median age at study of these 8 females was 31 years (range 21-64 years). Psychosis began in adolescence and adult life at a median age at onset of 21 years (range 11-28 years). When we analyzed our cohort aged 11 years (youngest age at onset of psychosis in our cohort) or older, we found that 8/39 (21%) were affected with a psychotic illness. The case histories of 2 women with *PCDH19*-GCE and a psychotic disorder are described in the Data S1.

The 8 females came from 7 families (Figure 1). Six (15%) had schizophrenia, of whom 2 were sisters (family D), 1 (3%) had a schizoaffective disorder, and 1 (3%) an "unspecified schizophrenia spectrum and other psychotic disorder" (Table 1). One female had childhood-onset

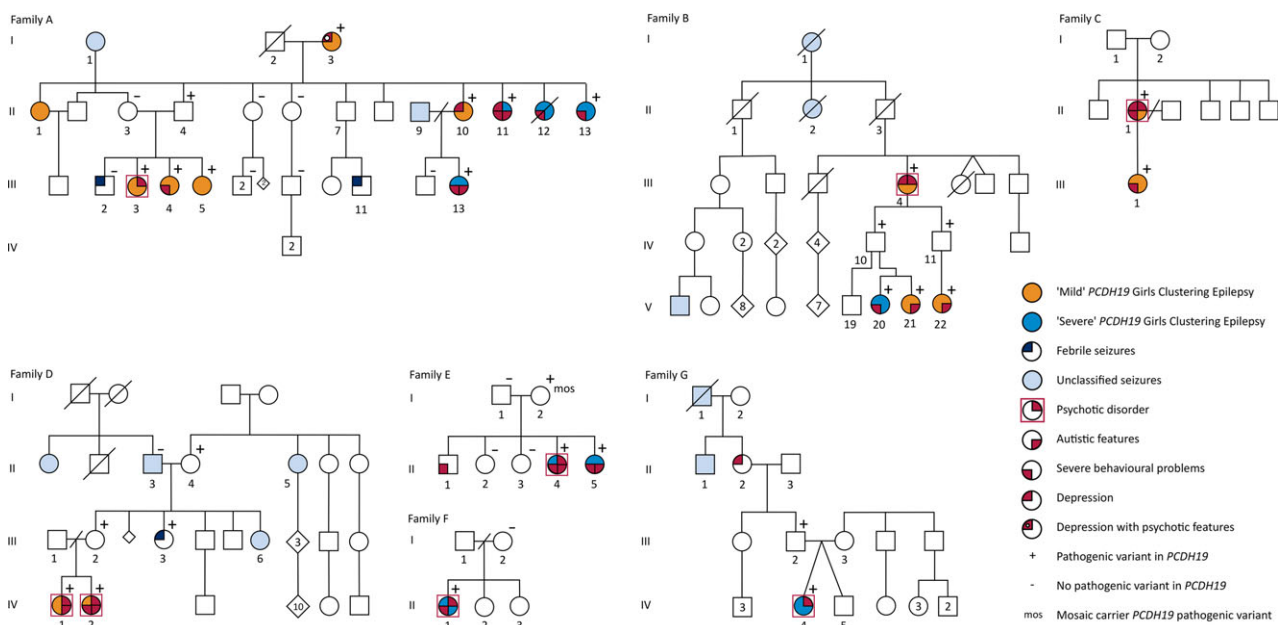


FIGURE 1 Pedigrees of 8 females with protocadherin 19 gene (*PCDH19*) Girls Clustering epilepsy (*PCDH19*-GCE) and psychotic disorders in 7 families. Females with a psychotic disorder are marked by a red box. Girls with mild *PCDH19*-GCE had mild epilepsy and intellectual disability (ID) and those with severe *PCDH19*-GCE had severe epilepsy and moderate to severe ID

TABLE 1 Schizophrenia and other psychotic disorders in 8 females with *PCDH19* pathogenic variants

	A:III:3 ^a	B:III:4 ^a	C:II:1	D:IV:1	D:IV:2	E:II:4	F:II:1	G:IV:4
Age at study (y)	25	64	35	29	21	27	23	27
Pathogenic variant, inheritance	p.Val441Glu, pat	p.Gln85*, UK	p.Lys708Argfs*9, UK	Exon 6 deletion, mat	Exon 6 deletion, mat	p.Leu25Pro, mat ^b	p.Ser845Asn, not mat	p.Arg911Gln, pat
Age at seizure onset; seizure types	12 m: GTCS	12 m: FS, GTCS	9 m: FMS, FIAS, CSE	14 m: FBTCs	19 m: T, FIAS, FBTCs	7 m: FS, GTCS, At, T, SE, FIAS	8 m: TCS	7 y: Abs, T, GTCS, AtAbs, FIAS
Development	Always delayed	-	Delay since 9 m	Delay since 14 m	Delay since 19 m	Yes	-	Delay noted at 3 y
Regression (age)	-	-	Yes (9 m)	Language (14 m), delay since	Yes (19 m)	Yes (7 m and language at 2 y)	-	Language (7 y)
Intellectual disability (IQ)	Mild (68)	No, but borderline intellect (77; VIQ 85, PIQ 72)	Mild	Mild (62; VIQ 61, PIQ 72)	Mild	Severe (20 single words)	Moderate (48-49)	Moderate
Psychiatric and behavioral problems before psychosis onset (age at onset)	-	UK	Depression, anxiety, aggression, self-injury, running away (21 y)	ASD (12 y)	Aggression and anxiety (<6 y), ASD (6 y)	Aggression, self-injury, anxiety (early age), ASD (3.5 y), running away (5 y)	Challenging behaviors and suicidal gestures (15 y)	-
Age at psychosis onset	23 y	21 y	28 y 10 m	20 y 4 m	18 y 2 m	11 y	19 y	19-20 y
Ongoing seizures at psychosis onset; seizure treatment	None for 15 y: no AED	Yes, two per year: AED	Yes: <u>CBZ</u> , <u>LEV</u>	Yes, 2-4 clusters yearly: <u>CLB</u> , <u>TPM</u> , <u>PHT</u>	Yes, single GTCS last year: AED	Yes, few yearly until 15 y: AED	Yes, breakthrough seizures with AED change: AED	Yes, every few weeks: <u>TPM</u> , <u>CLB</u> , <u>LTCG</u> , <u>VPA</u>
Duration of initial episode	Few months	12 m admitted	UK	1-2 wk	>1.5 y	Continuous	UK	5 y, following a SE
Delusions	Persecutory	Religious and grandiose	UK	-	Making up stories	-	-	Erotomanic
Hallucinations	Auditory	Auditory	UK	Auditory	-	Visual	Auditory	Auditory
Disorganized thinking	Poor cognitive insight	Irrational, poor cognitive insight	Threatened to cut out fetus	-	-	14 y: clear thought disorder for 2 wk while on RSP	-	Yes
Grossly disorganized or	↓Motor behavior	Sentenced for aggression to her child	UK	-	Catatonia (stands still for hours, excitable)	Behavioral deterioration with severe aggression	-	Aggression

(Continues)

TABLE 1 (Continued)

	A:III:3 ^a	B:III:4 ^a	C:II:1	D:IV:1	D:IV:2	E:II:4	F:II:1	G:IV:4
abnormal motor behavior								
Negative symptoms	Deterioration self-care, social withdrawal, alogia, flat affect	-	Dysthymia	-	Avolition, social withdrawal, alogia	-	-	-
Other symptoms related to psychotic symptoms	Suicidal ideation, anxiety, agoraphobia, panic	Grossly disorganized affect	UK	-	Decline in functioning and scholastic abilities	-	-	Psychotic event preceded by romantic obsession with cognitive regression
Treatment commenced after psychosis onset (effect) ^c	<i>TFP</i> , <i>VLF</i> , <i>CLP</i> , <i>CBZ</i> (noncompliant), admitted, <i>TFP depot</i> (±), <i>SRT</i> (+)	<i>TDZ</i> (+)	<i>RSP</i> (<i>noncompliant</i>), <i>RSP consta</i> (+), <i>OLZ</i> (+, <i>but briefly</i>)	-	<i>RSP</i> (+), <i>OLZ</i> (-), <i>LEV</i> (+)	<i>QTP</i> (-), <i>RSP</i> (-), Currently on: <i>OLZ</i> , <i>CLZ</i> , <i>FVX</i> (ongoing visual hallucinations)	UK (+)	<i>HLP</i> (sz.), <i>PHT</i> (-), <i>QTP</i> (+), <i>PRZ</i> (UK)
Recurrent psychotic episodes	24 y 7 m: Auditory hallucinations with suicidal ideation	25 y: Religious delusions, delusions of reference, hypomania and aggression	-30 y 4 m: Auditory hallucinations, aggression, social withdrawal, anhedonia with suicidal attempts, less sleep, anxiety, feelings of guilt	-21.5 y: Persecutory and religious delusions, auditory and visual hallucinations, fire-setting behavior, social withdrawal, deterioration self-care and alogia (mimicking a depression) for 1.5 y following a cluster of seizures	NA	NA	-23 y: Two relapses with hallucinations and behavioral deterioration -23 y: Disorientation, for which she was admitted a month	Frequent relapses when trying to reduce <i>QTP</i>
Seizures at last recurrence	None for 16 y	None for >1 y	None for >3 y	None for >4 y	NA	NA	Yes, breakthrough seizures	Yes, every few weeks (Continues)

TABLE 1 (Continued)

	A:III:3 ^a	B:III:4 ^a	C:II:1	D:IV:1	D:IV:2	E:II:4	F:II:1	G:IV:4
Treatment commenced after psychosis recurrences (effect) ^c	<i>RSP (galactorrhea)</i> , admitted, <u><i>OLZ (+)</i></u>	<i>CLP (+)</i>	<i>RSP (+)</i> , <u><i>DLX (+)</i></u> , <i>QTP (-)</i> , <u><i>PLP (UK)</i></u> , <u><i>HLP</i></u> with benzotropine (+)	<u><i>CZP (+)</i></u> , <u><i>RSP (±)</i></u> , <i>VPA (-)</i> , <u><i>OLZ (+, weight)</i></u> , <i>LEV (UK)</i> <u><i>APZ (-)</i></u> , <u><i>CLP (+)</i></u> , <u><i>HLP (+)</i></u>	NA	NA	<i>LMP (-)</i> , <i>ZPM (-)</i> . Currently stable on <u><i>VPA</i></u> , <u><i>LEV</i></u> , <u><i>HLP</i></u> with <u><i>procyclidine</i></u> , <u><i>APM</i></u>	-
Psychotic diagnosis	Schizophrenia	Schizoaffective disorder	Schizophrenia	Schizophrenia	Schizophrenia with catatonia	Schizophrenia	Unspecified	Schizophrenia
Psychiatric outcome	Multiple episodes, currently in remission with treatment. Ongoing PTSD with panic attacks after sexual assault	Multiple episodes with progressive worsening, currently in remission on treatment (occasional outbursts of aggressiveness)	Multiple episodes, currently in remission with treatment.	Multiple episodes, currently in remission with treatment. Ongoing major depressive disorder.	Single long episode, currently in remission with treatment.	Continuous hallucinations	Multiple episodes, currently in partial remission; persistent auditory hallucinations; sedated	Multiple episodes, currently in remission with antipsychotic treatment

Abs, absences; AED, antiepileptic drug; APM, alprazolam; APZ, aripiprazole; ASD, autism spectrum disorder; At, atonic seizures; AtAbs, atypical absences; CBZ, carbamazepine; CLB, clobazam; CLP, chlorpromazine; CZP, clonazepam; CSE, convulsive status epilepticus; DLX, duloxetine; FBTCs, focal to bilateral tonic-clonic seizures; FIAS, focal impaired-awareness seizures; FMS, focal motor seizures; FS, febrile seizures; FSQ, full-scale intelligence quotient; FVX, fluvoxamine; GTCS, generalized tonic-clonic seizures; HLP, haloperidol; ID, intellectual disability; IQ, intelligence quotient; LEV, levetiracetam; LMP, levomepromazine; m, months; mat, maternally inherited; LTG, lamotrigine; NA, not applicable; *OLZ*, olanzapine; pat, paternally inherited; PHT, phenytoin; PIQ, performance intelligence quotient; PLP, paliperidone; PRZ, prazosin; PTSD, posttraumatic stress disorder; QTP, quetiapine; RSP, risperidone; SE, status epilepticus; SRT, sertraline; T, tonic seizures; TCS, tonic-clonic seizure; TDZ, thioridazine; TFP, trifluoperazine; TPM, topiramate; UK, unknown; VLF, venlafaxine; VPA, valproate; VIQ, verbal intelligence quotient; wk, weeks; y, years; ZPM, zolpidem.

Underlined treatment is currently used. **Bold and italic** treatment concerns an antipsychotic drug. Mutations were reported according to transcript NM_001184880.¹

^aPatient has previously been published by Scheffer et al.¹

^bMother is mosaic for *PCDH19* pathogenic variant.

^cTreatment effect: -ineffective, +effective.

schizophrenia from age 11 years. Two had a coexisting psychiatric diagnosis; one had posttraumatic stress disorder (after a sexual assault) and another had a major depressive disorder.

In 7 women the initial episode of psychosis markedly varied in duration between 1 and 2 weeks and 5 years. The remaining woman (E:II:4) had frequent ongoing hallucinations from the age of 11 to 17 years. Six women had recurrent psychotic episodes. Psychotic symptoms included disorganized motor behavior (8) including catatonia in 1, hallucinations (7), delusions (6), negative symptoms (5), and disorganized thinking (3). Antipsychotic medication was commenced in all 8 females and was effective in all but 1 (E:II:4). Two females also had a positive response to a selective serotonin reuptake inhibitor (SSRI, sertraline) or to a selective serotonin-norepinephrine reuptake inhibitor (SNRI, duloxetine).

Three women had ASD diagnosed at age 3.5-12 years, 7-12 years before their presentation with psychosis; 5 women did not have a diagnosis of ASD. Behavioral problems in childhood or adolescence were already present before the onset of psychotic symptoms in 4 females and included aggression and anxiety (3), and behavioral problems with suicidal gestures (1). Only 1 female (C:II:1) was taking psychotropic medication, an antidepressant, and this was discontinued when she discovered she was pregnant, prior to onset of psychosis later in pregnancy.

The psychotic disorders occurred with comorbid ID in 7 of 8 females, which was mild in 4, moderate in 2, and severe in 1. The remaining patient had borderline intellect. A decline in scholastic abilities preceded psychotic symptoms in one adolescent (D:IV:2) aged 18 years with mild ID. A 19-year-old adolescent (G:IV:4) with moderate ID had cognitive regression associated with romantic obsessions; following an episode of status epilepticus, she developed erotomanic delusions. In 4 patients, social withdrawal was observed with the initial or recurrent episode of psychosis.

All 8 females had a history of seizures. In one woman, seizures had resolved 15 years before psychosis onset. The remaining 7 had ongoing seizures and were taking antiepileptic medication at the onset of psychosis. Seizures had resolved in 3 women 1 to 4 years before their psychosis recurred. For the 27-year-old woman (E:II:4) with childhood-onset schizophrenia beginning at age 11 years, seizures settled at age 15 years, although hallucinations persisted throughout adult life. The remaining 3 females had ongoing seizures including bilateral tonic-clonic seizures (3), focal impaired awareness seizures (2), tonic seizures (2), absences (1), and febrile seizures (1), with seizure frequencies varying from every few weeks to breakthrough seizures only associated with medication change. Results of neuroimaging performed in 7 of 8 patients (computed tomography [CT], 2; MRI, 5) were normal.

3.2 | Females with secondary psychotic symptoms (n = 2)

Two women in our cohort had psychotic symptoms that did not fulfil a diagnosis of a “schizophrenia spectrum or other psychotic disorder.” A 17-year-old adolescent with a de novo p.Glu201Pro *PCDH19* pathogenic variant (patient H) and moderate ID developed recurrent postictal psychosis, comprising auditory and visual hallucinations, following clusters of seizures from the age of 14 years. She has not yet received antipsychotic medication because her psychotic episodes have been postictal and self-limiting.

The matriarch of family A (Figure 1), Patient A:I:3, underwent abdominal surgery for a bowel obstruction at 75 years and developed major depression. Associated with this depression, she had ongoing psychotic features including visual hallucinations of people from her past hitting her. Treatment with citalopram, topiramate, and levetiracetam (the latter 2 for seizures) did not improve her depression or psychotic symptoms.

3.3 | Adolescents with serious behavioral problems (n = 3)

In the remaining 50 of 60 females without a psychotic disorder or psychotic symptoms, severe behavioral problems were present in 15 of 50 (30%). For 3 girls with moderate to severe ID, behavioral problems were extremely severe and disruptive to the families' lives in adolescence and adult life, rendering them housebound; and resulting in police visits to ensure safety due to the severity of the patient's aggression (Table 2). Behavioral problems began in childhood but became much more severe at age 10-12 years. Antipsychotic treatment was effective in one, ineffective in another, and whether antipsychotic treatment was prescribed for the third was not known. It was not possible to classify these behavioral problems as a schizophrenia spectrum or other psychotic disorder due to the lack of obvious signs of hallucinations or delusions in these adolescents with severe ID. Another girl (A:III:13) with severe ID developed extremely severe violent behavior twice following a midazolam intravenous treatment for anesthesia (<14 years) and for seizures (14 years).

3.4 | Genotype-phenotype correlation

No genotype-phenotype correlation for the occurrence of *PCDH19*-related psychotic and serious behavioral problems could be identified. The pathogenic variants of the 8 females with the psychotic disorders occurred throughout the gene and did not differ in location from those without psychotic disorders. The pedigrees show striking inter- and intrafamilial phenotypic heterogeneity of features including

TABLE 2 Grossly disorganized behavior in 3 females with a *PCDH19* pathogenic variant

	Patient B:V:20	Patient E:II:5	Patient I
Age at study (y)	17	15	13
Pathogenic variant, inheritance	p.Gln85*, paternal	p.Leu25Pro, mother mosaic	p.Asp412Gly, maternal ^a
Development	Delay since 11 m	Delay since 8 m	Always delayed
Regression (age)	Yes (11 m)	Yes (8 m)	Frequent regression with SE
Intellectual disability; speech	Severe: 20-30 single words	Moderate: limited speech	Severe: single words
Behavioral problems before deterioration (age at onset)	Tantrums, autistic features (since early age)	ADHD, OCD, ASD, aggression (<13 y)	Aggression and anxiety (since early age), ASD (12 y)
Age at seizure onset: seizure types	11 m: GTCS, FIAS, Abs, FS	8 m: T, FBTCs, aura, Abs, GTCS, CSE, FS	2 w: Abs, M, FIAS, UTCS, DA, spasms, SE
Age at onset behavioral deterioration	10 y	11-12 y	12 y
Seizures at behavioral deterioration onset: seizure treatment	Yes: <u>CBZ</u> , <u>CLB</u>	Yes, clusters every 6-8 w till 13 y: UK	Yes: <u>VPA</u> , <u>ZNS</u> , <u>CLB</u>
Initial presenting symptoms	Intermittent episodes of anger and difficult behavior characterized by tantrums, aggression, restlessness and self-injury	Cognitive and functioning deterioration with aggression to the point of requiring police intervention at home on multiple occasions and suspension from school	Cognitive and functioning deterioration from age 12 y with severe difficulties with transition, violence and aggression to the point that the family cannot leave the house.
Evolution of symptoms	16 y: easily frustrated, labile, inappropriate sexual touching of herself and others	Continuous intermittent aggression and running away	Continuous intermittent aggression
Treatment commenced for behavioral deterioration (effect) ^b	<i>HLP</i> (+), CLN (-), SRT (-), <i>QTP</i> (-)	<i>RSP</i> (UK). Currently on: <u>QTP</u> (-), <u>FVX</u> (-), <u>CLZ</u> (+), <u>TPM</u> (+)	<i>RSP</i> (<i>high prolactin</i>), <u>APZ</u> (-)

Abs, absences; ADHD, attention-deficit/hyperactivity disorder; APZ, aripiprazole; ASD, autism spectrum disorder; CBZ, carbamazepine; CLB, clobazam; CLN, clonidine; CZP, clonazepam; CSE, convulsive status epilepticus; DA, drop attack; FBTCs, focal evolving to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures; FS, febrile seizures; FVX, fluvoxamine; GTCS, generalized tonic-clonic seizures; HLP, haloperidol; M, myoclonic seizures; m, months; OCD, obsessive compulsive disorder; QTP, quetiapine; RSP, risperidone; SE, status epilepticus; SRT, sertraline; T, tonic seizures; TPM, topiramate; UK, unknown; UTCS, unknown onset tonic-clonic seizures; VPA, valproate; wk, weeks; y, years; ZNS, zonisamide.

Underlined treatment is currently used. **Bold and italic** treatment concerns an antipsychotic drug. Variants were reported according to transcript NM_001184880.¹

^aThis girl also has a p.Ser218Leu pathogenic variant in *CACNA1A* that was not maternally inherited.

^bTreatment effect: -ineffective, +effective.

a spectrum of severity for epilepsy, ID, behavioral, and psychiatric problems including psychotic disorders (Figure 1).

4 | DISCUSSION

PCDH19-related epilepsies typically present in infant girls who have clusters of seizures, often triggered by fever. The term *PCDH19* Girl Clustering Epilepsy has been

recently suggested to aid in earlier recognition of this serious disorder.^{4,13,14} The psychiatric features in childhood and adolescence of severe behavioral problems, obsessional features, and ASD often prove more disabling for patients and families, even though seizures may have abated.¹ Here, we have described 8 females with *PCDH19*-GCE who present with adolescent- or adult-onset psychotic disorder with prominent decline in functioning, of whom 6 satisfied a diagnosis of schizophrenia.

4.1 | Psychotic disorders in *PCDH19*-GCE

We studied the presence of psychotic disorders in 60 females with *PCDH19*-GCE. Because psychosis presented from the age of 11 years, we calculated the frequency in our 39 older females aged 11 years or older. We found that 21% of our older cohort developed psychotic disorders, most often classified as schizophrenia (15% of total). This 21% figure is a minimum estimate of the frequency of psychotic disorders. Fourteen (36%) of the 39 females are still younger than 29 years of age, which was the oldest age of onset of psychosis in our cohort.

Diagnosis of psychotic disorders in patients with comorbidities can be challenging. First, psychotic episodes in patients with ongoing seizures are often considered postictal phenomena. However, 4 of 8 females developed their initial or recurrent psychotic symptoms when they had been seizure-free for at least a year, such that their psychosis could not be considered postictal. Guidelines for the diagnosis of postictal psychosis indicate that the duration of psychosis should be less than 2 months, yet for 3 of our remaining 4 females with psychotic illness, the psychosis lasted from 18 months to 16 years.^{20,21} Second, 3 other women had concurrent behavioral or social deterioration with psychosis, supporting a diagnosis of a “schizophrenia spectrum or other psychotic disorder.”

Third, psychotic symptoms such as changes in thinking and speech are more difficult to recognize in patients with ID. Although the women with mild ID or borderline intellect presented with a typical thought disorder, the woman with severe ID (E:II:4) had more subtle observable changes such as looking and smiling at the corners of a room. This was coupled with a major change in behavior at age 11 years, presenting with severe aggression and running away from school. Not included in the 8 patients with psychotic disorders was a 19-year-old nonverbal adolescent with severe ID who developed odd postictal behavioral changes such as laughing at the toilet bowl. This behavior was observed on only 2 occasions and was insufficient to meet diagnostic criteria for a psychotic disorder.

Only one other female with *PCDH19*-GCE and psychosis has been reported,¹⁰ in addition to our original report of 2 cases; the latter 2 are included in the 8 patients reported here (Table 1).^{1,2} The lack of additional published cases with psychotic disorders may be explained by the young age of the majority of girls with *PCDH19*-GCE. Recognition of this disease is rapidly increasing, with greater access to genetic testing for children with infantile-onset seizures. In addition, many adolescent and adult women with ID and seizures are not offered genetic testing, despite recommendations for clinical testing.^{22,23} Moreover,

the association of psychosis in a woman with a history of seizures in childhood may not be considered as related to an underlying *PCDH19* pathogenic variant, even where the variant is known. Currently, there are 9 *PCDH19* mosaic males reported in the literature, of whom 7 had behavioral problems, but they are too young (only 3 were aged 13 and 14 years) to determine whether they are at risk of psychosis.^{5,6,24,25} Longer-term follow-up of women and mosaic men with *PCDH19*-GCE will clarify the risk of later-onset psychotic disorders.

It is possible that the severe behavioral problems seen in *PCDH19*-GCE could be a precursor to later-onset psychotic disorders in some patients (Table 2). In 3 additional adolescents with moderate to severe ID, we observed horrific and grossly disorganized behavioral problems. It is uncertain whether their behavioral regression in puberty could reflect thought disorder that is difficult to decipher given the severity of their cognitive impairment.

4.2 | Frequency of psychotic disorders in *PCDH19*-GCE

The frequency of psychotic disorders (21%), including schizophrenia (15%), in our cohort of females with *PCDH19* pathogenic variants was far higher than general population estimates of psychotic disorders (3.5%) and schizophrenia (1.4%) in the Finnish National Population Register.²⁶ The frequency is also higher than that found in cohorts with ID, ASD, or epilepsy, where risk is elevated. In individuals with ID, the prevalence of psychotic disorders was 4.4% in a cohort of 1023 patients²⁷ and the prevalence of schizophrenia was 3.6% of 13 295 patients.²⁸ For patients who have ASD without ID, schizophrenia spectrum disorders occurred in 6% of 713 patients.²⁹ Turning to epilepsy, psychosis (not further classified) was diagnosed in 5.6% of patients in a meta-analysis of 56 studies including more than 40 000 participants and was most frequent in those with temporal lobe epilepsy (7%).³⁰

Risk for psychotic disorders in females with *PCDH19*-GCE appears to be more comparable to that of individuals with rare recurrent microdeletions and microduplications that are associated with schizophrenia.³¹ These include chromosome 22q11.2 deletions where schizophrenia and schizophrenia spectrum disorders develop in up to 25% of patients,³² and 15q13.3 deletions where 10.2% are reported to have schizophrenia.³³ Other lower-risk copy number variants have been reported in large-scale population studies.^{34,35}

Why only one-fifth of women with *PCDH19*-GCE develop psychotic disorders remains to be elucidated. Our patients had pathogenic variants throughout *PCDH19*: in exon 1 (4), 2 (1), and 5 (1) and deletions in exon 6 (2). Larger numbers of affected women may enable genotype-phenotype correlations to emerge.

4.3 | Possible shared mechanisms between psychosis and *PCDH19*-GCE

There may be shared disease mechanisms explaining the increased risk of psychosis in *PCDH19*-GCE, based on observations relating to hormonal manipulation and brain connectivity. First, psychotic disorders often begin in adolescence, when hormonal levels in the hypothalamus-pituitary-adrenal axis change.³⁶ Lower blood levels of allopregnanolone, an important neurosteroid, are found in patients with psychosis and also in females with *PCDH19*-GCE.^{37–39} Furthermore, differences in neurosteroid levels between patients with *PCDH19* pathogenic variants and controls become more evident in puberty, when psychosis has its onset.³⁹ Pilot clinical trials of allopregnanolone showed a positive effect on schizophrenia-related symptoms and cognition in patients with schizophrenia.⁴⁰ A single open-label pilot study of ganaxolone, a synthetic neurosteroid, in 11 children with *PCDH19*-GCE showed improved seizure control, but the effect on behavior and psychiatric symptoms has not been studied.⁴¹ Second, reduced connectivity in perceptual and executive networks has been shown in schizophrenia.⁴² *PCDH19* encodes a cell-cell adhesion molecule and mosaic *Pcdh19* murine expression results in differential adhesion of neural progenitor cells and abnormal arrangement and sorting of cells during cortical development that likely disturb connectivity of the brain.⁴ Brain network connectivity studies in females with *PCDH19* pathogenic variants may shed light on the human correlate and the networks involved may aid in predicting risk for the development of schizophrenia.

4.4 | Psychotic disorders as later-onset manifestation of genetic disease

The concept of a later-onset phenotype has been recognized in other genetic disorders. For instance, males who carry the fragile X premutation are unaffected until late adult life when they may develop fragile X-associated tremor/ataxia syndrome.⁴³ Adolescents with Dravet syndrome due to an *SCN1A* pathogenic variant often develop a crouch gait, whereas adults may develop Parkinsonian features in their 30s.^{44,45} Such later-onset disorders will only become recognized with more access to genetic testing of older individuals, and with longitudinal observation of patients with specific genetic diseases as they age.

4.5 | Limitations

This study has several limitations. It would be ideal to have the same psychiatrist see all patients; however, this is impossible as the patients are in different regions of the world, and the episodes of psychosis have occurred over

many years. In addition, we do not have scores on neuropsychological subscales (verbal, nonverbal, memory, processing speed, and attention), and testing would be challenging in some of the patients given their severe behavioral disturbance and severity of cognitive impairment. Looking at changes in these domains before, during, and after psychotic episodes would help to understand the course of these disorders in patients with *PCDH19*-GCE.

5 | CONCLUSIONS

We identified schizophrenia and other psychotic disorders as a later-onset manifestation of *PCDH19*-GCE, occurring in one-fifth of female older adolescents and women. Monitoring, recognition, and appropriate treatment of later-onset schizophrenia in females with *PCDH19*-GCE should become part of routine care in this population.

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DISCLOSURE OF CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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