

Diagnosis and misdiagnosis of adult neuronal ceroid lipofuscinosis (Kufs disease)



Samuel F. Berkovic, MD, FRS
John F. Staropoli, MD, PhD
Stirling Carpenter, MD
Karen L. Oliver, MSc
Stanislav Kmoch, PhD
Glenn W. Anderson, MSc
John A. Damiano, BSc
Michael S. Hildebrand, PhD
Katherine B. Sims, MD
Susan L. Cotman, PhD
Melanie Bahlo, PhD
Katherine R. Smith, PhD
Maxime Cadieux-Dion, BSc
Patrick Cossette, MD, PhD
Ivana Jedličková, MSc
Anna Přistoupilová, MSc
Sara E. Mole, PhD
On behalf of the ANCL Gene Discovery Consortium

Correspondence to
Dr. Berkovic:
s.berkovic@unimelb.edu.au

Supplemental data
at Neurology.org

ABSTRACT

Objective: To critically re-evaluate cases diagnosed as adult neuronal ceroid lipofuscinosis (ANCL) in order to aid clinicopathologic diagnosis as a route to further gene discovery.

Methods: Through establishment of an international consortium we pooled 47 unsolved cases regarded by referring centers as ANCL. Clinical and neuropathologic experts within the Consortium established diagnostic criteria for ANCL based on the literature to assess each case. A panel of 3 neuropathologists independently reviewed source pathologic data. Cases were given a final clinicopathologic classification of definite ANCL, probable ANCL, possible ANCL, or not ANCL.

Results: Of the 47 cases, only 16 fulfilled the Consortium's criteria of ANCL (5 definite, 2 probable, 9 possible). Definitive alternate diagnoses were made in 10, including Huntington disease, early-onset Alzheimer disease, Niemann-Pick disease, neuroserpinopathy, prion disease, and neurodegeneration with brain iron accumulation. Six cases had features suggesting an alternate diagnosis, but no specific condition was identified; in 15, the data were inadequate for classification. Misinterpretation of normal lipofuscin as abnormal storage material was the commonest cause of misdiagnosis.

Conclusions: Diagnosis of ANCL remains challenging; expert pathologic analysis and recent molecular genetic advances revealed misdiagnoses in >1/3 of cases. We now have a refined group of cases that will facilitate identification of new causative genes. [Neurology® 2016;87:579-584](https://doi.org/10.1212/WNL.0000000000002584)

GLOSSARY

ANCL = adult-onset neuronal ceroid lipofuscinosis; **CGP** = custom gene panel; **NCL** = neuronal ceroid lipofuscinosis; **WES** = whole-exome sequencing.

Diagnosis of neurodegenerative diseases in younger adults is challenging due to the relative rarity of the problem, the heterogeneous causes, and the frequent absence of noninvasive diagnostic clues, raising the question of brain biopsy. The neuronal ceroid lipofuscinoses (NCLs) are a group of storage diseases presenting from infancy to adulthood.¹ The stored material is largely made up of subunit c of mitochondrial adenosine triphosphate synthase or saposin proteins A and D—that is, of proteins so hydrophobic that they require special mechanisms for their breakdown and disposal.²

Adult-onset NCL (ANCL) is a particularly demanding diagnostic problem. Childhood NCLs have well-characterized clinical patterns typically involving brain and eye, abundant storage in readily accessible peripheral tissues such as skin, and largely solved molecular genetic causes.³⁻⁵ In contrast, ANCL can present in a variety of ways with progressive myoclonus epilepsy, dementia, or motor disorders and shows limited storage in peripheral tissue. Stored material is usually only found in a subset of neurons, with the accumulation of age-related lipofuscin

From the Epilepsy Research Centre, Department of Medicine (S.F.B., K.L.O., J.A.D., M.S.H.), University of Melbourne, Austin Health, Heidelberg, Australia; Biogen, Inc. (J.F.S.), Cambridge, MA; Department of Pathology (S.C.), Centro Hospitalar São João, Porto, Portugal; Institute of Inherited Metabolic Disorders (S.K., I.J., A.P.), First Faculty of Medicine, Charles University in Prague; General University Hospital in Prague (S.K.), Czech Republic; Great Ormond Street Hospital for Children NHS Foundation Trust (G.W.A.), London, UK; Center for Human Genetic Research and Department of Neurology (K.B.S., S.L.C.), Harvard Medical School, Massachusetts General Hospital, Boston; Population Health and Immunity Division (M.B., K.R.S.), The Walter and Eliza Hall Institute of Medical Research; Departments of Mathematics and Statistics and Medical Biology (M.B.), University of Melbourne, Australia; Centre de Recherche du Centre Hospitalier de l'Université de Montréal (M.C.-D., P.C.), University of Montreal, Canada; and MRC Laboratory for Cell Biology (S.E.M.), Department of Genetics, Evolution & Environment and UCL Institute of Child Health, University College London, UK.

Coinvestigators are listed on the [Neurology®](http://Neurology.org) Web site at Neurology.org.

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often confused with pathologic storage.^{6–13} Furthermore, molecular genetic characterization of ANCL is at an early stage. Hindered by the small number of cases, and the clinical and pathologic challenges, ANCL is poorly understood.

Kufs disease is the best-known form of ANCL; it differs from most childhood-onset forms because there is no retinal involvement, and the inheritance can be either recessive or dominant. It is widely accepted that the uncommon teenage-onset cases without retinal involvement are grouped with adult-onset cases. The clinical presentation is variable with 2 broad forms identified. Kufs type A presents with progressive myoclonus epilepsy, whereas Kufs type B presents with dementia and motor signs.^{6,13} Recessive mutations in *CLN6*^{14–16} and dominant mutations in *DNAJC5*^{17–19} can cause Kufs type A; Kufs type B can be caused by recessive mutations in *CTSF*.^{20,21} Rare cases of ANCL with retinal involvement are described due to mutations in *PPT1 (CLN1)*,^{22,23} *CLN5*,^{24,25} and *GRN*.²⁶ Finally, some patients

with *CLN3* mutations present with neurologic manifestations in adult life, on a background of visual failure in childhood.²⁷

Despite these important molecular discoveries, many reported cases that receive a diagnosis of ANCL remain unsolved. As ANCL is rare, we formed a consortium to combine putative unsolved cases from centers around the world and analyzed them as one large cohort. We aimed to refine the clinical spectrum of late-onset NCL by implementing an expert clinical and pathologic review process, followed by consensus diagnosis. Here we report our somewhat surprising results, in particular, the frequent misdiagnosis of a broad spectrum of neurologic disorders as Kufs disease. Our eventual aim is to discover the remaining molecular causes of ANCL.

METHODS Participants. We established the ANCL Gene Discovery Consortium encompassing researchers with clinical, neuropathologic, and molecular genetic expertise in ANCL from the United Kingdom, Europe, United States, Canada, and Australia.

Consortium members pooled 47 unrelated, unsolved cases into a shared database. These cases had been referred to individual Consortium researchers for molecular genetic studies over a 20-year period because of diagnosis or putative diagnosis of ANCL. Clinicopathologic support for an ANCL diagnosis varied considerably in these cases that remained unsolved despite study by a variety of molecular genetic and enzymatic assays over time. For familial cases, only the proband was included. No attempt was made to sequence all known NCL genes before entry into the study.

Standard protocol approvals, registrations, and patient consents. Local institutional review boards at each contributing site approved this research. Participants or their guardians provided informed consent.

Diagnostic criteria. We developed initial diagnostic criteria based on a combination of clinical and pathologic features. These criteria were based on review of the literature and the clinical experience of Consortium members.^{6–13}

Clinical and pathologic review of cases. Strenuous attempts were made to source detailed clinical data from treating clinicians. We deliberately used broad clinical criteria (table 1) that allowed for retinal involvement.

Neuropathologic diagnosis remains the gold standard for this group of disorders. A panel of 3 expert neuropathologists (J.F.S., S.C., G.W.A.) developed criteria to classify the pathologic data as definite, probable, or possible NCL (table 1). Images of the pathologic material, where available, were subsequently shared with each of the 3 neuropathologists. They provided independent opinions, which were then discussed, and a consensus on the classification reached.

Overall classification of cases. Each case was given a final classification of definite ANCL, probable ANCL, possible ANCL, or not ANCL based on clinical and pathologic data. This occurred via regular Consortium teleconferences where the clinical criteria and pathologic classification were integrated to determine an overall classification (table 2).

Table 1 Adult-onset neuronal ceroid lipofuscinosis: Clinical and pathologic criteria

Clinical criteria (all 4 criteria required)
Age at onset between 12 and 60 years
Normal development and cognition prior to disease onset
Presence of at least 2 of the following: Seizures or myoclonus Progressive cognitive decline Ataxia Pyramidal or extrapyramidal motor signs
Documented deterioration over more than 2 years
Pathologic criteria
Definite pathologic features
Ultrastructural demonstration of one or more characteristic membrane-bound storage morphologies (granular osmiophilic deposits [GRODs], fingerprint profiles, curvilinear profiles, or rectilinear complexes) in more than one cell type, including but not limited to eccrine secretory and duct cells, endothelial cells, smooth and skeletal muscle cells, or neurons or their proximal axons. Fingerprint profiles in vascular smooth muscle and pericytes are excluded, since it has been shown that they accumulate there nonspecifically with aging ³⁵
Probable pathologic features
Ultrastructural demonstration of one or more characteristic membrane-bound storage morphologies (GRODs, fingerprint profiles, curvilinear profiles, or rectilinear complexes) in a single cell type AND Demonstration, in standard histologic preparations, of cytoplasmic inclusions with broad-range autofluorescence or Luxol fast blue positivity in well-differentiated sections in one or more of above cell types, to a degree significantly greater than expected for age, OR Demonstration, by standard immunohistochemistry, of characteristic cytoplasmic storage material, i.e., subunit c of mitochondrial adenosine triphosphate synthase, saposin protein A, or saposin protein D
Possible pathologic features (in absence of ultrastructural data)
Demonstration, in standard histologic preparations, of cytoplasmic inclusions with broad-range autofluorescence or Luxol fast blue positivity in well-differentiated sections in one or more of the above cell types, to a degree significantly greater than expected for age

Table 2 Adult-onset neuronal ceroid lipofuscinosis (ANCL) classification criteria incorporating both clinical and pathologic criteria (see table 1) for 47 putative cases

ANCL classification	Clinicopathologic criteria	No. of cases
Definite ANCL	All clinical criteria met plus definite pathology classification	5 ^a
Probable ANCL	Atypical clinical presentation (e.g., late onset) plus definite pathology classification All clinical criteria met plus probable pathology classification	2
Possible ANCL	Atypical clinical presentation plus probable pathology classification All clinical criteria met plus possible pathology classification	9
Not ANCL	Clinical, pathologic, or molecular data strongly suggesting an alternate diagnosis Review of images or source material suggests no evidence of neuronal ceroid lipofuscinosis Pathology images unavailable (i.e., report only)	31

^aOne case had a compound heterozygous *CLN6* mutation.

Molecular genetic studies. Screening for known ANCL genes (*CLN6*, *CTSF*, *DNAJC5*, *GRN*, and *PPT1*) was performed by both Sanger sequencing and high-throughput sequencing technologies in the majority of the 16 cases (detailed in table

e-1 on the *Neurology*[®] Web site at Neurology.org). Genomic DNA was extracted from venous blood using standard methods. Briefly, for Sanger sequencing, coding exons and flanking intronic regions including splice sites of the 3 genes were PCR amplified using primers designed for all isoforms with reference human gene transcripts (NCBI Gene; <http://www.ncbi.nlm.nih.gov/>; primers available on request). Amplification reactions were cycled on a Veriti Thermal Cycler (Applied Biosystems, Carlsbad, CA) and bidirectional sequencing was completed using BigDye v3.1 Terminator Cycle Sequencing Kit (Applied Biosystems). Sequencing products were resolved using a 3730xl DNA Analyzer (Applied Biosystems). Sequence chromatograms were compared to published cDNA sequence with nucleotide changes detected using Codon Code Aligner (CodonCode Corporation, Dedham, MA).

A custom gene panel (CGP), designed to target coding regions (6.88 Mb) of 3,616 OMIM genes with known phenotypes including ANCL, and whole-exome sequencing (WES) was also performed for the majority (table e-1). DNA enrichment was performed according to the manufacturer's protocol using either SeqCap EZ Choice Library (Roche Nimblegen, Madison, WI) for the CGP or Nimblegen SeqCap V3 (Roche Nimblegen) for WES. DNA sequencing was performed on the captured barcoded DNA libraries using either SOLiD 4 System (Applied Biosystems) or

Table 3 Summary of 10 cases with an initial diagnosis of adult-onset neuronal ceroid lipofuscinosis (ANCL) in which an alternate diagnosis was later confirmed

Case	Clinical features	Initial ANCL diagnosis	Diagnostic reevaluation	Final diagnosis
KC23	Onset mid-20s with motor and intellectual deterioration (dementia); no seizures; progressive ataxia but no distinct chorea; autosomal dominant family history	Clinical history consistent with ANCL; skin biopsy interpreted as showing fingerprint profiles	Pathology review: normal lipofuscin; clinical review suggested Huntington disease; genetic diagnosis: <i>HTT</i> expansion	Huntington disease
KC33	Onset 28 years with cognitive decline; seizure history unknown; deceased in 40s	Clinical history consistent with ANCL; brain biopsy interpreted as showing autofluorescent inclusions and GROD-like material	Pathology review: Normal lipofuscin; genetic diagnosis: <i>NPC1</i> mutation	Niemann-Pick syndrome
KC51	Onset 34 years; dementia with frontal features, subtle facial dyskinesia, parkinsonian and mild cerebellar features including limb ataxia; no seizures; autosomal recessive family history	Clinical history consistent with ANCL; skin biopsy interpreted as showing fingerprint profiles in sweat glands	Pathology review: normal lipofuscin; genetic diagnosis: <i>PLA2G6</i> p.G551S mutation	Neurodegeneration with brain iron accumulation
KC35	Onset 20s with progressive cognitive decline followed by tremor, myoclonus, and ataxia	Clinical history consistent with ANCL; skin biopsy interpreted as showing membrane-bound inclusions with granular material	Pathology review: images of source material not available; genetic diagnosis: <i>c19orf12</i> mutation	Neurodegeneration with brain iron accumulation
KC10	Onset age 29 with rapidly progressing dementia, motor deterioration, and myoclonus	Clinical history consistent with ANCL; rectal biopsy identified electron-dense structure interpreted as fingerprints and curvilinear pattern consistent with NCL	Pathology review: images of source material not available; brain biopsy revealed malignant lymphocytes	Cerebral Lymphoma
KC24	Onset 22 years; myoclonus and tonic-clonic seizures; cognitive decline; personality change; unsteady gait from early 20s leading to wheelchair dependence; deceased at 26 years	Clinical history consistent with ANCL; postmortem brain biopsy interpreted as consistent with ceroid lipofuscinosis	Pathology review: extensive lesion of the thalamus consistent with "familial" fatal insomnia; immunohistochemistry: PrP ^{Sc} positive; genetic diagnosis: <i>PRNP</i> insertion c.154_177[6_13]	Prion disease
KC29	Onset at 13 years with myoclonus; tonic-clonic seizures and absences at 15 years; progressive ataxia; wheelchair-bound at 22 years; late ophthalmoplegia; mild learning disability	Clinical history consistent with ANCL; skin and muscle biopsy negative	Pathology review: images of source material not available; genetic diagnosis: hypothesis free whole exome sequencing showed <i>SACS</i> p.P2798Q; p.T458I mutation ³⁶	Autosomal recessive spastic ataxia of Charlevoix-Saguenay
KC8	Onset at 33 years with gait ataxia and subsequent dementia, dystonia, and psychiatric symptoms; no seizures; autosomal dominant family history	Clinical history consistent with ANCL; premortem biopsies not done	Autopsy revealed classical Alzheimer disease; genetic diagnosis: <i>PSEN1</i> p.S170F; <i>CTSD</i> p.A58V ³⁷	Early-onset familial Alzheimer disease
KC21	Onset at 13 years with behavioral changes (frontal dysfunction) and declining school performance; myoclonus with occasional tonic-clonic seizures and poor coordination	Clinical history consistent with ANCL; no pathology (biopsy not done)	Genetic diagnosis: hypothesis free whole exome sequencing showed <i>SERPINI1</i> p.G392E mutation ³⁶	Neuroserpinopathy
KC7	Onset age 19 years; progressive disease with myoclonus, epilepsy, and ataxia	Clinical history consistent with ANCL; skin, muscle, and brain biopsy negative	Pathology review: images of source material not available; genetic diagnosis: <i>MTND3</i> mutation	Leigh syndrome

Illumina HiSeq 1500. Data analysis was performed as previously described.²⁸ The data were inspected for variations in known ANCL genes and the search for novel genes is ongoing.

Molecular diagnosis of cases initially suspected of having ANCL, where other disorders were later established, were performed at a number of commercial and research laboratories using standard techniques.

RESULTS Of the 47 Consortium cases, 16 cases fulfilled the Consortium's clinical and pathologic criteria for definite, probable, or possible ANCL disease (table 2). Of the 16 cases, 8 (2 definite) presented with seizures as a main feature, usually with a progressive myoclonus epilepsy (Type A Kufs). The remaining 8 cases (3 definite) presented with dementia and motor signs (Type B Kufs). None of the ANCL cases had retinal involvement. The mean age at onset was 35 years (median 35.5 years). There were 2 clusters; 6 had onset in the second decade of life and 10 in the fourth decade or later. Both Type A and Type B cases were represented in the 2 age clusters. Two cases fell outside of our arbitrary 12- to 60-years range for disease onset (onset at 10 and 62 years); these cases were considered clinically atypical and classified overall as possible ANCL (table 2).

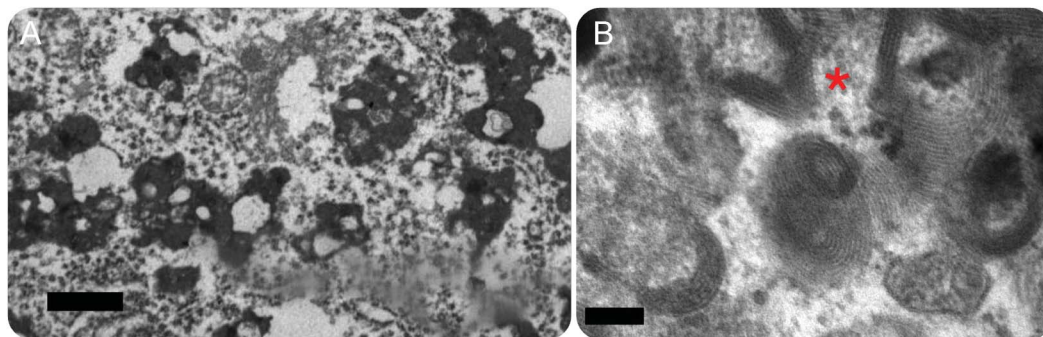
A family history suggestive of dominant inheritance was found in 4/16 ANCL cases; in 12, there was no family history. *DNAJC5* mutations were not found in the 4 dominant cases or the 10 other cases that had this gene sequenced. *CLN6* and *CTSF*, known causes of recessive ANCL, were sequenced in 15 cases and 1 case had probable pathogenic compound heterozygous *CLN6* variants identified. This patient was classified as definite ANCL with a Type A presentation. This leaves a subset of 15 genetically unsolved ANCL cases (4 definite).

Our criteria for ANCL were not met in 31/47 (66%) cases, including 2 cases previously published in detail as having ANCL.^{29,30} In 10 of these 31 cases, detailed review with further investigation established definitive alternate diagnoses (table 3). The main reason for misdiagnosis as ANCL was overinterpretation of normal age-related lipopigment as pathologic storage material (figure). Six cases had features suggesting that ANCL was not the correct diagnosis. Two of these had storage material without the characteristics of the lipopigment seen in NCL, but a specific diagnosis could not be made. Two had other neuropathologic abnormalities, again without leading to a specific diagnosis. In 2 cases, biopsy material reported as suggestive of NCL was considered nonspecific on review, and the clinical features were atypical. In the remaining 15 cases, the clinical and pathologic data were inadequate for classification.

DISCUSSION In this study of 47 cases considered to have ANCL, we found that the diagnosis could be supported in only 16 cases; of these, 9 were considered possible cases. Moreover, ANCL was confidently excluded in 16 cases, of which 10 had secure alternative diagnoses established. The classification criteria developed by the Consortium were useful in formalizing the approach to problematic cases and has highlighted the challenges and subtleties in diagnosing ANCL.

The pathologic diagnosis is challenging and is compounded by the relative rarity of these disorders such that most neuropathologists have very limited experience with the condition. In general, misdiagnosis occurred by overinterpretation of ultrastructural findings in biopsy samples, with failure to distinguish

Figure Pathologic diagnosis and misdiagnosis of adult-onset neuronal ceroid lipofuscinosis (ANCL)



(A) Electron micrograph of KC33 shows one of many deposits of lipofuscin in a cortical neuron. These deposits were originally considered to represent granular osmiophilic deposits (GRODs), leading to a diagnosis of ANCL. Lipid vacuoles, as seen here, are numerous in lipofuscin, but not in GRODs, and the granules in lipofuscin are coarser and less uniform (bar = 5 μ m). The patient had cognitive decline beginning at age 28 years; *NPC1* mutation was later found (table 3). (B) This electron micrograph of KC15 shows fingerprint profiles from an eccrine secretory cell. The basic paired parallel line pattern even at this magnification tends to appear as a single wide slightly fuzzy line, but the spacing, the wheeling ranks, and the focal crystalline pattern where the ranks intersect (at the left of the asterisk) are very characteristic (bar = 1 μ m). Disease onset was at 18 years with stimulus-sensitive and action-induced myoclonus, dementia, and parkinsonism on the background of normal development. This case met out criteria for classification as definite ANCL. The molecular basis remains unknown.

normal lipofuscin that accumulates with age, from abnormal lipopigment seen in NCL, which may be very limited in ANCL.^{6–13} In children, this distinction is easier, contrasting abundant storage in disease with minimal normal age-related pigment. Rather than relying on the amount of lipopigment, accurate diagnosis depends on analysis of the particular ultrastructural features.^{7,31} In all late-onset neuronal storage diseases, only a subset of neurons may be involved. This becomes important when it comes to electron microscopy on a brain biopsy. If the blocks have not been trimmed to include involved neurons, the study may be limited to normal neurons that inevitably contain lipofuscin, and confusion with ANCL may result.

Importantly, the removal of these cases from the cohort helps simplify the apparent clinical and pathologic heterogeneity of ANCL. The clinical profile of our ANCL cases fit broadly into the previously described categories of presentation as progressive myoclonus epilepsy (Type A) and dementia with motor disturbances (Type B)⁶; the single case that was solved molecularly with a *CLN6* mutation had a Type A presentation, as has been previously described.¹⁴

The degree of genetic heterogeneity of ANCL remains unclear. It is already known that contrary to the childhood forms, which are essentially all recessive disorders, the adult forms can have either recessive or dominant inheritance.^{6,32,33} While it is now possible to survey the whole exome (or genome) for genetic variation with high-throughput sequencing technology, determining which of the many thousand variants identified are pathogenic remains challenging. However, this is still a good option for treating clinicians and may avoid the need for brain biopsy should a plausible variant be found in one of the known ANCL genes or in a gene known to cause an alternative late-onset neurologic disease. The efficacy of genetic testing for diagnostic purposes will only improve as further ANCL genes are discovered. At this point in time, pathologic diagnosis remains the gold standard practice.

Future research into the underlying genetic etiology of the unsolved ANCL will be supported by the removal of misdiagnosed cases that would hinder these important efforts. By pooling together unrelated ANCL cases that putatively may share the same causative gene, the genomic search space can be considerably narrowed. This ongoing work, resulting in a deeper understanding of the molecular genetic basis, will provide improved guidance for the accurate and early diagnosis of ANCL. We anticipate that the recently accepted nomenclature for the NCL³⁴ will be expanded as new genes are identified.

AUTHOR CONTRIBUTIONS

Dr. Berkovic drafted/revised the manuscript for content, contributed to study concept/design, contributed to acquisition of the data, performed analysis/interpretation of the data, and provided study supervision and

coordination. Dr. Staropoli revised the manuscript for content, contributed to study concept/design, contributed to acquisition of the data, performed analysis/interpretation of the data, and provided study coordination. Dr. Carpenter revised the manuscript for content and performed analysis/interpretation of the data. K.L. Oliver drafted/revised the manuscript for content, contributed to acquisition of the data, performed analysis/interpretation of the data, and provided study coordination. Dr. Kmoch revised the manuscript for content, contributed to study concept/design, contributed to acquisition of the data, and performed analysis/interpretation of the data. G.W. Anderson revised the manuscript for content and performed analysis/interpretation of the data. J.A. Damiano revised the manuscript for content and performed analysis/interpretation of the data. Dr. Hildebrand revised the manuscript for content and performed analysis/interpretation of the data. Dr. Sims revised the manuscript for content, contributed to acquisition of the data, and performed analysis/interpretation of the data. Dr. Cotman revised the manuscript for content, contributed to acquisition of the data, and performed analysis/interpretation of the data. Dr. Bahlo revised the manuscript for content and performed analysis/interpretation of the data. Dr. Smith revised the manuscript for content and performed analysis/interpretation of the data. M. Cadieux-Dion revised the manuscript for content and performed analysis/interpretation of the data. Dr. Cossette revised the manuscript for content and contributed to acquisition of the data. I. Jedličková revised the manuscript for content and performed analysis/interpretation of the data. A. Přistoupilová revised the manuscript for content and performed analysis/interpretation of the data. Dr. Mole revised the manuscript for content, contributed to study concept/design, contributed to acquisition of the data, performed analysis/interpretation of the data, and provided study coordination.

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DISCLOSURE

S. Berkovic has served on scientific advisory boards for UCB and Janssen-Cilag; serves on the editorial boards of *Lancet Neurology* and *Epileptic Disorders* and the Advisory Board of *Brain*; may accrue future revenue on pending patent WO61/010176: Therapeutic Compound that relates to discovery of PCDH19 gene as the cause of familial epilepsy with mental retardation limited to females; is one of the inventors listed on a patent held by Bionomics Inc. on diagnostic testing using the *SCN1A* gene, WO2006/133508; has received speaker honoraria from UCB; has received unrestricted educational grants from UCB, Janssen-Cilag, and Sanofi-Aventis; and receives/has received research support from the National Health and Medical Research Council of Australia and NINDS. J. Staropoli, S. Carpenter, K. Oliver, S. Kmoch, G. Anderson, J. Damiano, M. Hildebrand, K. Sims, S. Cotman, M. Bahlo, K. Smith, M. Cadieux-Dion, P. Cossette, I. Jedličková, A. Přistoupilová, and S. Mole report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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