New ICD-10-CM code proposal for KCNQ2-related epilepsy

John J. Millichap, MD, FAAP, FAAN, FAES, FACNS

Pediatric Epileptologist
Adjunct Associate Professor of Neurology
Northwestern University Feinberg School of Medicine

On behalf of KCNQ2 Cure Alliance

KCNQ2-related epilepsy is a common neonatal-onset epilepsy syndrome

- **KCNQ2-related epilepsy was described in 1998** and is not a new disorder.
- Caused by variants in the **KCNQ2 gene**, encoding a neuronal potassium channel subunit.
- Occurs with an estimated incidence of **1 in 17,000 live births**.
- **One of the most common genetic epilepsy syndromes in childhood**, among the top 3 genetic diagnosis in epilepsy, and the most frequent cause of seizures of genetic origin **presenting within the first month of life**.

© 1998 Nature Publishing Group http://www.nature.com/naturegenetics

article

A novel potassium channel gene, *KCNQ2*, is mutated in an inherited epilepsy of newborns

Nanda A. Singh[1], Carole Charlier[1], Dora Stauffer[1], Barbara R. DuPont[2], Robin J. Leach[2], Roberta Melis[3], Gabriel M. Ronen[4], Ingrid Bjerre[5], Thomas Quattlebaum[6], Jerome V. Murphy[7], Malcolm L. McHarg[8], David Gagnon[9], Teodoro O. Rosales[10], Andy Peiffer[1], V. Elving Anderson[11] & Mark Leppert[1]

ORIGINAL ARTICLE

KCNQ2 Encephalopathy: Emerging Phenotype of a Neonatal Epileptic Encephalopathy

Sarah Weckhuysen, MD,[1,2,3] Simone Mandelstam, MB ChB,[4,5] Arvid Suls, PhD,[1,2] Dominique Audenaert, PhD,[1,2,6] Tine Deconinck, MSc,[1,2] Lieve R.F. Claes, PhD,[1,2] Liesbet Deprez, PhD,[1,2] Katrien Smets, MD,[1,2,7] Dimitrina Hristova, MD,[8] Iglika Yordanova, MSc,[9] Albena Jordanova, PhD,[1,2] Berten Ceulemans, MD, PhD,[2,10] An Jansen, MD, PhD,[11,12] Danièle Hasaerts, MD,[11] Filip Roelens, MD,[13] Lieven Lagae, MD, PhD,[14] Simone Yendle, BSc (Hons),[15] Thorsten Stanley, MD,[16] Sarah E. Heron, PhD,[17] John C. Mulley, PhD,[18,19] Samuel F. Berkovic, MD, FRS,[15] Ingrid E. Scheffer, MBBS, PhD,[4,15,20] and Peter de Jonghe, MD, PhD[1,2,7]

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

ELSEVIER

Antiepileptic therapy approaches in *KCNQ2* related epilepsy: A systematic review

M. Kuersten[a], M. Tacke[a,c], L. Gerstl[a,c], H. Hoelz[a,c], C.v. Stülpnagel[a,b,c], I. Borggraefe[a,c,*]

[a] Division of Pediatric Neurology, Developmental Medicine and Social Pediatrics, Dr. von Haunersches Children's Hospital, LMU Munich, Lindwurmstraße4, 80337, Munich, Germany
[b] Paracelsus Medical University, Salzburg, Austria
[c] Comprehensive Epilepsy Center for Children, Adolescents and Adults, LMU Munich, Lindwurmstraße 4, 80337, Munich, Germany

A unique and clearly defined disorder

- **KCNQ2-related epilepsy has a distinctive pathophysiology that manifest in a characteristic clinical course:**
  - Early-onset **epilepsy** (most frequent cause in the first month of life)
  - Variable degrees of initial **drug-refractoriness** that later diminishes
  - Moderate to profound **developmental delay** that persist even when seizure freedom is achieved
  - **EEG abnormalities**, which progress from a burst suppression pattern to multifocal epileptiform activity and to slow EEG background
- **Presents with a range of severities. Recognized by ILAE** as a severe KCNQ2 developmental and epileptic encephalopathy (KCNQ2-DEE) and self-limited (familial) neonatal epilepsy (SeLNE) (Zuberi et al., 2022).

This profile **differentiates it from other infantile-onset epilepsies**

Separate medical entity and diagnosis

KCNQ2-related epilepsy is regarded as a separate medical entity and diagnosis by clinicians, the patient community and drug development purposes:

- Although missing an ICD-10-CM code, it is **included in several medical classifications** such as the NIH Genetic and Rare Diseases Information Center (GARD 13060) and European Orphanet classification for rare disease nomenclature (ORPHA:439218).
- The ILAE recently recognized KCNQ2-related epilepsy as part of the classification and definition of epilepsy syndromes with onset in neonates and infants.
- FDA has granted **Orphan Drug Designation, Fast-Track Designation and Rare Pediatric Disease Designation** to two different treatments in development for KCNQ2-related epilepsy.
- FDA has authorized a **pivotal clinical trial** (NCT04639310, ongoing) that will lead to a potential marketing authorization indicated for patients with KCNQ2-related epilepsy.

Having an ICD-10-CM code **will facilitate patient access to these treatments** after eventual approval

Unique medical needs

Patients with KCNQ2-related epilepsy have unique medical needs that differ dramatically from other epilepsy syndromes and therefore not captured by current epilepsy (G40) codes:

- Relative **unresponsiveness to the first line medications** most often used in other forms of neonatal-onset epilepsy (phenobarbital, benzodiazepines, levetiracetam).
- Partial favorable response to epilepsy drugs acting on sodium channels, **which are otherwise little-used in the Neonatal Intensive Care Unit,** and are contraindicated for other epilepsies like Dravet syndrome.
- **Unique evolution of epilepsy in this disorder**, characterized by very early-onset followed by seizure remission with persistent developmental impairments, unlike most infantile-onset epilepsies.
- Unlike other epilepsy syndromes, patients with KCNQ2-related epilepsy also require multidisciplinary **management of their developmental and communication comorbidities** that is uniquely tailored to the disorder.

Why an ICD-10-CM code is needed now

- Currently **impossible to use ICD-10-CM codes** to specify the patient's actual diagnosis (KCNQ2-related epilepsy) and the relevant gene (KCNQ2), which makes tracking difficult.
- Having a unique code will enhance **adoption of recommended treatments.**
- Current need to use multiple and varying codes for associated conditions leads to inconsistent tracking across visits, and having a unique code will enhance tracking for clinical care and research studies.
- Importantly, with an ongoing Phase 3 clinical trial indicated for patients with KCNQ2-related epilepsy, approving a specific ICD-10-CM code now is critical for patient **access to potential near-future treatments**.

Having a unique ICD-10-CM code will directly help KCNQ2-related epilepsy patients, enabling easier access to various services and treatments