Familial *KCNQ2* mutation: a psychiatric perspective

Anton Iftimovici[a,b], Angeline Charmet[c], Béatrice Desnous[d], Ana Ory[c], Richard Delorme[c], Charles Coutton[e], Françoise Devillard[e], Mathieu Milh[d] and Anna Maruani[c]

KCNQ2 mutations are a common cause of early-onset epileptic syndromes. They are associated with heterogeneous developmental profiles, from mild to severe cognitive and social impairments that need better characterization. We report a case of an inherited *KCNQ2* mutation due to a deletion c.402delC in a heterozygous state, in the exon 3 of the *KCNQ2* gene. A 5-year-old boy presented a cluster of sudden-onset generalized tonic-clonic seizures at three months of age, after an unremarkable postnatal period. Multiplex ligation-dependent probe amplification identified a familial mutation after an investigation in the family revealed that this mutation was present on the father's side. The patient was diagnosed with autism and intellectual deficiency in a context of *KCNQ2*-encephalopathy. We describe his clinical features in light of current literature. This report highlights the importance of appropriate genetic counseling and psychiatric assessment in planning the medical and social follow-up of a disorder with complex socio-behavioral features. *Psychiatr Genet* 34: 24–27

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[a]Université Paris Cité, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, "Physiopathology of psychiatric disorders" team, [b]GHU-Paris Psychiatrie et Neurosciences, Hôpital Sainte Anne, [c]Department of Child and Adolescent Psychiatry, Robert Debré Hospital, APHP, Paris, [d]Aix Marseille University, Department of pediatric neurology, La Timone Children's Hospital, Marseille and [e]Laboratoire de Génétique Chromosomique, Service de Génétique, Génomique et Procréation, Centre Hospitalier Universitaire Grenoble-Alpes, Université Grenoble-Alpes, Grenoble, France

Correspondence to Anton Iftimovici, MD, PhD, Pôle hospitalo-universitaire d'Évaluation, Prévention, et Innovation Thérapeutique (PEPIT), Hôpital Sainte-Anne, GHU-Paris Psychiatrie et Neurosciences, 1 Rue Cabanis, 75014 Paris, France
Tel: +01 45 65 81 79; e-mail: anton.iftimovici@ghu-paris.fr

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Background

KCNQ2 mutations can lead to a range of heterogeneous early-onset epileptic syndromes, from self-limited familial neonatal epilepsy to severe neonatal-onset developmental and epileptic encephalopathy. Additional features may include dystonia, spasticity, cortical visual impairment, abnormal eye movements, or feeding intolerance (Morrison-Levy *et al*., 2021). *KCNQ2* is one among the genes coding for *KCNQ* M-current potassium channels that assemble as heteromers, controlling adaptation of neuronal firing and spike frequency across the brain (Delmas and Brown, 2005; Soh *et al*., 2022). The overall incidence of *KCNQ2*-related disorders is estimated at 2.93–3.59 per 100 000 births (López-Rivera *et al*., 2020). Functional outcome is highly variable with different patterns of seizure activity (some subsequently affecting brain maturation) on the one hand, and altered neurodevelopment on the other, independently of epilepsy. Moreover, different mutations of the *KCNQ2* gene can cause the same phenotype (Milh *et al*., 2016). In this context of heterogeneous genotype/phenotype relationships, the spectrum of *KCNQ2*-related neurodevelopment extends from normal cognition to severe motor, behavioral and social impairment (Symonds *et al*., 2019). However, although the available literature draws an increasingly clearer picture of the various epileptic syndromes and developmental profiles, there is a need to improve our understanding of the socio-behavioral aspects of the disease to inform and prepare families and caregivers. This is especially important in the long-term as seizure frequency usually declines or recedes after childhood, while a high frequency of autistic features and mild to severe intellectual disability (ID) are reported among adults with *KCNQ2* encephalopathy (Boets *et al*., 2022).

Case presentation

We describe the clinical trajectory of a 5-year-old boy who presented at three months with a cluster of sudden-onset generalized tonic-clonic seizures, over a period of 10 days, efficiently treated with sodium valproate 20 mg/kg for 15 months with full recovery and no further antiepileptic medication required. His father reported similar early-onset generalized tonic-clonic seizures during childhood in the first weeks after birth, efficiently treated with antiepileptics, and followed by a typical neurodevelopment. An investigation in the family revealed that a *KCNQ2* mutation was already known on the paternal grandfather's side. Further contacting the estranged part of the family on this side, the parents learned that many of the family members also presented with various levels

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of neurodevelopmental delays. At 5 months, a multiplex ligation-dependent probe amplification confirmed the familial deletion c.402delC (p.IIe134Metfs*37, NM_172107.2) in a heterozygous state, in the exon 3 of the *KCNQ2* gene. At age 2, psychomotor regression occurred: he became silent, social response could not be elicited anymore, and he developed an important food selectivity to certain colors and textures. While a diagnosis of *KCNQ2*-related encephalopathy was retained at the time, there had been no formal assessment of the autistic traits. Educational help was provided with a carer dedicated to him in kindergarten but without autism-specific accommodations. At age four, because of persistent behavioral rigidity and disabling sensory particularities, the parents reached out to a *KCNQ2* patient association, who subsequently referred them to our specialist autism outpatient unit, where the patient underwent an extensive neuropsychiatric assessment. We received him at age 5. He measured 1.06 m for 17.3 kg, with 52 cm head circumference. General physical and neurological examination was unremarkable. Socially, the patient gave initially no attention to adults, had no joint attention, was avoidant, but allowed a limited interaction after a period of habituation. He demonstrated hetero-aggressivity when frustrated. Our extensive assessment is described in Table 1. It led to a diagnosis of autism spectrum disorder (ASD) and ID with severe delay in cognitive, adaptive abilities, and speech (less than 1 year of equivalent developmental age). The confirmation of the ASD diagnosis provided the patient with an ASD-specific schooling orientation in anticipation of primary school. The assessment of his level of ID helped the various caregivers find the most appropriate rehabilitation or adaptive techniques for his intellectual age.

Discussion

KCNQ2-related disorders are usually diagnosed in the neonatal period, as the vast majority of patients start with stormy epilepsy, which begins in the first week of life (Weckhuysen *et al.*, 2012; Milh *et al.*, 2013). This mode of onset is quite similar in both self-limited and severe forms. The present report indicates that this specific mutation seems to lead to a relatively late epilepsy onset for a disorder related to *KCNQ2*, with self-limiting epilepsy that no longer persists. Epilepsy and neurodevelopmental disorders seem thus to develop independently. Despite the deletion of an exon, we do not know whether it resulted in a truncated protein or a complete loss of function, although a single base deletion in exon 3 has been shown to lead to a frameshift and the synthesis of a truncated protein (Lauritano *et al.*, 2019). For missense mutations, the correlation between severity and genotype is less straightforward than for truncating and stop mutations (Soldovieri *et al.*, 2014). Most of the latter lead to self-limited forms with or without slight developmental disorder, generally leading to mild cognitive impairment. Missense mutations are associated with a much wider range of phenotypes (Weckhuysen *et al.*, 2012). This heterogeneity is partly related to the biological effect of the mutation. Indeed, in some cases, there is a relationship between the impact of the mutation on the IM current and the intensity of the neurodevelopmental disorder (Miceli *et al.*, 2013). In other cases, the severity seems to be related to an abnormal channel distribution on the neuronal membrane (Abidi *et al.*, 2015). These functional consequences exert a dominant negative effect. More recently, gain-of-function mutations have been described. Epilepsy either is delayed or absent, and the neurodevelopmental disorder is very variable with a high prevalence of ASDs (Mulkey *et al.*, 2017). Interestingly, phenotypes associated with recurrent mutations have been described in detail. Despite the similarity of the *KCNQ2* mutation, the phenotype may be extremely variable, indicating that factors other than those related to the KCNQ2 mutation may be involved in the phenotype of patients (Miceli *et al.*, 2022).

The study of patients and models of *KCNQ2* opens fascinating perspectives for the understanding of the link between visible epilepsy and developmental disorders. This link is not causal. In animal models, cognitive impairment is not prevented by treating seizures, but by correcting the mutation or its effects before it becomes

Table 1 **Neuropsychiatric and psychological assessment**

Domain	Behavior	Sensoriality	Social interaction	Level of development	Adaptive behavior
Scales	ADHD rating scale: 38 Aberrant behavior checklist: 165 Repetitive behavior scale: 63	Dunn sensory profile: Touch processing: 11 Olfactory procession: 11 Auditory filtering: 15 Visual processing: 16 Energy: 25	Social responsiveness scale: 118, T = 79 Autism diagnostic interview-revised - Social interaction: 31 - Communication (non-verbal): 14 - Restricted, repetitive behaviors: 16 - Onset before 36 months: 5 Autism diagnostic observation schedule-2 - Social affect: 19 - Restricted, repetitive behaviors: 6 - Total: 25 - Comparison score: 9	Mullen scale (in months) Visual perception: 14 Fine motor skills: 22 Receptive speech: 2 Expressive speech: 9	Vineland scale (percentiles) Communication < 1% Daily life < 1% Socialization < 1% Motricity < 1% Standard result < 1%

ADHD: attention deficit and hyperactivity disorder: cut-off = 28. Social responsiveness scale: cut-off = T > 60. Autism diagnostic interview revised (ADI-R): social interaction cut-off = 10; communication non-verbal cut-off = 7; restricted, repetitive behaviors cut-off = 3, onset before 36 months cut-off = 1. Autism diagnostic observation schedule (ADOS): total cut-off = 7.

symptomatic (Peters *et al.*, 2005; Marguet *et al.*, 2015). In humans, the link between epileptic activity and cognitive profile has not yet been proven (Berg *et al.*, 2022). Recently, the study of an animal model of severe KCNQ2-related disorder showed that the impact of the mutation on the IM current was limited in time. Indeed, the IM current was abnormal until the age of weaning, causing neuronal hyperexcitability. After weaning, the current normalized, the neuronal hyperexcitability disappeared, while the seizures persisted and the cognitive disorders became measurable (Biba-Maazou *et al.*, 2022). Overall, current data tend to show: (1) that the disorder induced by the mutation occurs earlier than the seizures (which are a late reflection of it); (2) that treating the seizures will probably not be sufficient to allow normal development; and (3) that at the stage of cognitive and/or autistic disorders, the target is no longer IM, but late co-consequences of the earlier dysfunction of IM. The study of the effects of the mutation on the early stages of development (establishment of protomaps, first neuronal assemblies, first network activities; impact on critical periods of development…) opens an unexplored field to better understand the emergence of the autistic disorder in this condition and in general (Cossart and Garel, 2022). When mutations are associated with highly variable phenotypes between a parent and child, the possibility that the parent carries a somatic mosaic has been raised (Milh *et al.*, 2015). Here, this possibility is excluded because of the transmission over several generations.

This patient's history is relevant for psychiatric and social reasons as well. A main issue of care in this case was the diagnostic delay. First, the molecular diagnosis was delayed by the fact that the existence of a familial mutation was initially unknown to the parents. This raises the question of guilt and stigma around genetic diagnoses and the reasons not to disclose them to other members of the family. Thus, it has been reported that people with epilepsy could experience genetic information as harmful for a variety of reasons from fear of health insurance eligibility and loss of coverage for their children, to how this may change one's view of reproduction, or significant guilt in parents who may have transmitted the genetic risk (Shostak *et al.*, 2011). Thus, felt stigma was found to be increased by genetic causal attribution of epilepsy (Sabatello *et al.*, 2015; Garofalo *et al.*, 2019). A specialist genetic counseling should therefore systematically be offered to families, especially as the diagnosis itself provides many benefits not only in terms of early healthcare but also as a reducer of self-blame and uncertainty. By improving their understanding of the disease, patients can regard it as something they are not responsible for in terms of lifestyle (Shostak *et al.*, 2011). Second, there was a delay in the subsequent diagnosis of ASD. ASD is frequently associated with KCNQ2-related diseases and is directly attributable to the mutation (Cheng *et al.*, 2021; Siracusano *et al.*, 2022). Early screening is an important goal as it opens the way to specialized ASD-oriented care, such as applied behavior analysis therapy, while allowing families to benefit from adapted schooling. In the context of precision medicine, these interventions are crucial to assess and improve the quality of life of patients with developmental and epileptic encephalopathies, which require personalized, individually based assessment tools of clinical outcome and communication abilities (Berg *et al.*, 2022; Cohen *et al.*, 2022).

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Conflicts of interest

There are no conflicts of interest.

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