



## A novel *KCNQ3* mutation in familial epilepsy with focal seizures and intellectual disability

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### SUMMARY

Mutations in the *KCNQ2* gene encoding for voltage-gated potassium channel subunits have been found in patients affected with early onset epilepsies with wide phenotypic heterogeneity, ranging from benign familial neonatal seizures (BFNS) to epileptic encephalopathy with cognitive impairment, drug resistance, and characteristic electroencephalography (EEG) and neuroradiologic features. By contrast, only few *KCNQ3* mutations have been rarely described, mostly in patients with typical BFNS. We report clinical, genetic, and functional data from a family in which early onset epilepsy and neurocognitive deficits segregated with a novel mutation in *KCNQ3* (c.989G>T; p.R330L). Electrophysiological studies in mammalian cells revealed that incorporation of *KCNQ3* R330L mutant subunits impaired channel function, suggesting a pathogenic role for such mutation. The degree of functional impairment of channels incorporating *KCNQ3* R330L subunits was larger than that of channels carrying another *KCNQ3* mutation affecting the same codon but leading to a different amino acid substitution (p.R330C), previously identified in two families with typical BFNS. These data suggest that mutations in *KCNQ3*, similarly to *KCNQ2*, can be found in patients with more severe phenotypes including intellectual disability, and that the degree of the functional impairment caused by mutations at position 330 in *KCNQ3* may contribute to clinical disease severity.

**KEY WORDS:** Benign familial neonatal seizures, *KCNQ*, Cognitive impairment, Voltage-gated potassium channels, Epilepsy, Mutagenesis, Genotype-phenotype correlations.



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Mutations in the *KCNQ2* gene encoding for neuronal potassium channel subunits cause neonatal epilepsies with wide phenotypic heterogeneity, ranging from benign familial neonatal seizures (BFNS) with normal cognition and unremarkable neuroimaging,<sup>1,2</sup> to early onset epileptic encephalopathy with mental retardation, suppression-burst electroencephalography (EEG), and distinct neuroradiologic features.<sup>3</sup> On the other hand, mutations in *KCNQ3*, encoding for channel subunits forming heteromeric *KCNQ2/KCNQ3* potassium channels underlying the M-current<sup>4</sup> have been only rarely described, mostly in families affected with benign epilepsy with variable age of onset and good outcome. More recently, however, a *KCNQ3* mutation has been found in two siblings with neonatal seizures and intellectual disability.<sup>5</sup> Clinical, genetic, and functional characterization of a family (Fig. 1A) in which epilepsy and

neurocognitive deficits segregated with a novel mutation in *KCNQ3* is reported.

## METHODS

### Standard protocol approvals and patient consent

The institutional review boards of the University of Palermo and of the “G. Gaslini” Institute provided ethical approval. All participants provided written informed consent.

### Cognitive evaluation

Cognitive assessment was performed using the age-appropriate Wechsler Scale of Intelligence.

### Genetic analysis

The probands (individuals III:1 and III:2) were screened for *KCNQ2* and *KCNQ3* mutations by direct sequencing of amplified genomic DNA. Variants were classified as mutations according to previously described criteria.<sup>5</sup>

### Mutagenesis and heterologous expression of *KCNQ2* and *KCNQ3* subunits

Mutations were engineered by QuikChange mutagenesis (Stratagene, Milan, Italy) in human *KCNQ3* complementary DNA (cDNA) (NM\_004519.2) cloned into pcDNA3.1.<sup>6</sup>

Plasmids were transiently transfected in Chinese Hamster Ovary (CHO) cells using Lipofectamine 2000 (Invitrogen, Milan, Italy).

### Whole-cell electrophysiology

Macroscopic current recordings from CHO cells and data analysis were performed as described.<sup>6</sup> In the experiments with tetraethylammonium (TEA), currents were activated by 3-s voltage ramps from  $-80$  mV to  $+20$  mV at 0.08-Hz frequency. TEA blockade was expressed as the percentage of peak current inhibition produced by a 2-min drug application.

### Statistics

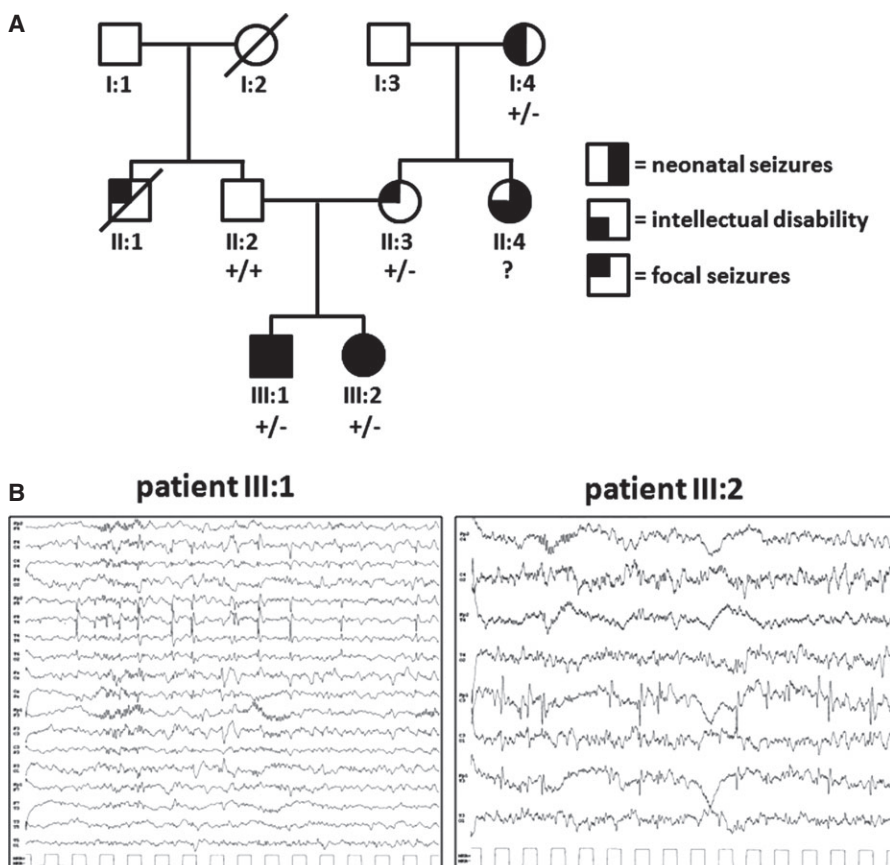
Data are expressed as the mean  $\pm$  standard error of the mean (SEM). Statistically significant differences were evaluated with the Student's *t*-test ( $p < 0.05$ ) and indicated with appropriate symbols.

## RESULTS

### Case descriptions

#### Individual III:1

This 12-year-old boy was born at 38 weeks of gestation after uneventful pregnancy and spontaneous delivery. Birth weight was 2900 g, height 54 cm, and head circumference



**Figure 1.**

Pedigree of the family and EEG of the two affected siblings. **(A)** Pedigree of the family. “+” = wild-type *KCNQ3* allele; “-” = mutant *KCNQ3* allele; “?” indicates DNA not available. **(B)** Interictal sleep EEGs showing focal sharp waves and sharp waves complex over the right frontocentral regions in patient III:1 (left) and biphasic spike and spike wave complexes over the left frontotemporal areas in patient III:2 (right).

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35.5 cm. From day 2 to day 4 of life, the patient experienced clusters of focal seizures characterized by staring and clonic manifestations involving asymmetrically the four limbs, and was treated with phenobarbital. Head control, sitting without support, and walking were achieved at 4, 7 and 18 months, respectively. He spoke words at 12 months and two-word phrases at 30 months. At 36 months of life, 6 months after phenobarbital withdrawal, the patient experienced four focal tonic-clonic seizures preceded by right head deviation and staring, at awakening. Valproic acid was started and the boy remained seizure-free up to the age of 10 years, when he manifested occasional episodes of right or left hemiclonic seizures during sleep. At that time, his EEG revealed sharp waves and sharp wave complex over the right frontotemporal areas increased by drowsiness on normal background activity (Fig. 1B, left). Neurologic examination showed clumsiness without gross neurologic deficits. At 11 years and 3 months, he showed mild intellectual disability (ID) (full scale IQ 53, 99% confidence interval [CI] 47–63; verbal IQ 47, 99% CI 41–61; performance IQ 70, 99% CI 63–83). His academic skills remained impaired and he received permanent educational support at school. Brain magnetic resonance imaging (MRI) performed at 8 years of age was unremarkable. The patient remained seizure-free by increasing the daily dose of valproic acid (30 mg/kg/day).

#### Individual III:2

This 9-year-old girl was born at term from unrelated parents after an uneventful pregnancy and delivery. Her birth weight was 2700 g. At day 2 of life she presented a cluster of focal seizures characterized by staring and clonic movements involving asymmetrically the four limbs, successfully treated with phenobarbital. At age 4 months she experienced a cluster of right hemiclonic seizures during sleep, treated with valproate. Head control, sitting without support, and walking were achieved at 4, 8, and 24 months, respectively. The girl spoke her first words at 3 years, and subsequent acquisition of developmental milestones was mildly slowed. At 4 years of age, she began to have monthly right hemiclonic seizures during sleep and isolated, brief dyscognitive seizures occurring mainly at awakening. Brain MRI performed at 4 years of age was unremarkable. Interictal EEG, performed at 6 years and 9 months of age, revealed normal background activity and asynchronous biphasic spike and spike wave complexes increasing during sleep, more evident over the left frontotemporal areas (Fig. 1 B, right); as was the case for individual III:1, neonatal EEG for III:2 is not available. Neurologic examination showed mild dysmetria and ataxia, nystagmus, and fine motor difficulties. The girl easily engaged in activities and played with simple toys and exhibited oppositional behavior and hyperactivity. She had severe language impairment with phonetic-phonologic difficulties, poor vocabulary, and two-word phrases. Cognitive assessment showed severe ID (full scale IQ 38, 99% CI 37–50; verbal IQ 45, 99% CI 42–57;

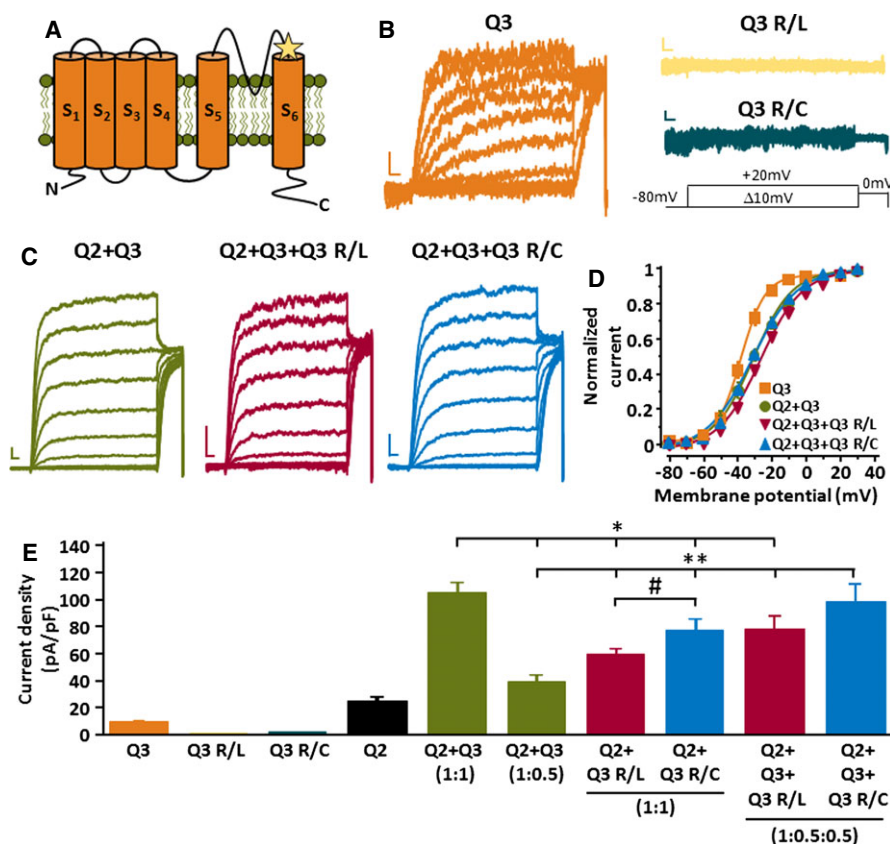
performance IQ 40, 99% CI 37–53). At the last evaluation, her academic skills remained impaired and she was receiving permanent educational support at school. She is seizure-free on carbamazepine (20 mg/kg/day) and valproate (25 mg/kg/day).

#### Additional family members

The mother of the siblings (II:3), currently 42-year-olds, with no history of neonatal seizures, experienced occasional brief focal seizures with staring and right head and eye deviation, sometimes followed by secondary generalization from age 10 years and disappearing 2 years later without treatment. Her intellectual assessment revealed a global IQ at the lower level of the normal range (full scale IQ 71, verbal IQ 65, performance IQ 85); her EEG is normal, and she engages in a work activity and takes care of her family. The father of two patients (II:2) is a 40 year old man with an unremarkable personal clinical history; he engages in a work activity, his EEG is normal, and the intellectual assessment displays a global IQ level within the normal range (full scale IQ 98, verbal IQ 82, and performance IQ 119). The grandmother (I:4) is a 64-year-old woman who did not have neonatal seizures but experienced rare motor seizures from 14 years of age; her intellectual assessment shows mild cognitive impairment (full scale IQ 69, verbal IQ 68, performance IQ 77). Individual II:4, the sister of II:3, currently 36-years-old, had neonatal-onset seizures remitting after 3 months; she also displayed moderate cognitive impairment (full scale IQ 50, verbal IQ 48, performance IQ 63). Additional family history is unremarkable, except for individual II:1, who had focal recurrent motor and tonic-clonic seizures beginning at age of 40 days following brain injury and lasting until 34 years of age, when he died accidentally.

#### Genetic and functional studies

A c.989G>T mutation in *KCNQ3*, causing a leucine substitution of the highly conserved arginine residue at position 330 in the pore-forming region, immediately before the sixth putative transmembrane domain S6 (Q3 R/L; Fig. 2A), was found in III:1, III:2, II:3, and I:4, but not in individual II:2; DNA from individual II:4 was not available. No *KCNQ2* mutation was detected in the probands. A different *KCNQ3* mutation at position 330 (R330C; Q3 R/C) has been described in families showing typical BFNS features including age of onset and remission of seizures, sensitivity to AEDs, no recurrence of seizures after the neonatal period, and normal neurocognitive development.<sup>7,8</sup> Heterologously expressed homomeric Q3 channels generated slowly activating voltage-dependent K<sup>+</sup> currents; by contrast, cells expressing Q3 R/L or R/C mutant subunits failed to generate detectable currents (Fig. 2B). However, mutant subunits could be partially rescued in heteromeric channels when expressed with *KCNQ2* (Q2) subunits (Q2:Q3mut cDNA ratio 1:1) (Fig. 2E). Maximal current size at 0 mV was larger in Q2 + Q3 R/C than in Q2 + Q3 R/L heteromeric channels (Fig. 2E). Heteromerization of Q2 with Q3



**Figure 2.**

Schematic representation of a KCNQ subunit topology and functional analysis of *KCNQ3* mutations at position 330. **(A)** Schematic drawing of a single KCNQ subunit. Transmembrane segments are indicated as S1–S6. The star indicates the R330 position. **(B,C)** Macroscopic currents from the indicated homomeric **(B)** or heteromeric **(C)** channels. In **(B)** current scale 20 pA, time scale 100 msec; in **(C)** current scale 200 pA, time scale 100 msec. **(D)** Conductance/voltage curves. Continuous lines are Boltzmann fits.<sup>5</sup> **(E)** Average current densities from the indicated channels. \*,  $p < 0.05$  versus Q2+Q3 (1:1); \*\*,  $p < 0.05$  versus Q2+Q3 (1:0.5); #,  $p < 0.05$  versus Q2+Q3 R/L. Note the statistically significant difference in current density between Q3 R/C- and Q3 R/L-containing heteromers. Number in parenthesis indicate the transfected cDNA ratios (Q2:Q3:Q3mut).  $n = 13$ –24 cells per group recorded in at least three separate experimental sessions.

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subunits is known to reduce current sensitivity to TEA blockade;<sup>4</sup> in fact, the percent of currents blocked by 3 mM TEA was  $87.8 \pm 3$ ,  $8 \pm 2$ , and  $48.8 \pm 4.2$  in Q2, Q3, and Q2 + Q3 channels, respectively ( $n = 6$ –13;  $p < 0.05$ ). Current blockade by 3 mM TEA (in %) was  $71.2 \pm 2.1$  and  $64.6 \pm 2$  in Q2 + Q3 R/L and Q2 + Q3 R/C channels, respectively ( $n = 6$ –13); these values were higher than those of Q2 + Q3 channels, and different from each other ( $p < 0.05$ ). Altogether, these results suggest that Q3 R/L subunits produce greater functional deficits than R/C subunits in heteromeric channels with Q2.

To mimic the genetic condition of the affected patients who carry a single Q3 mutant allele, CHO cells were also transfected with Q2 + Q3 + Q3 R/L or Q2 + Q3 + Q3 R/C cDNAs at a 1:0.5:0.5 ratio. When compared to heteromeric Q2 + Q3 channels, current density from Q2 + Q3 + Q3 R/L-transfected cells was significantly reduced; by contrast, we were unable to detect significant changes in macroscopic

current density between cells transfected with Q2 + Q3 + Q3 R/C and Q2 + Q3 (Fig. 2E). No changes in gating steady-state properties could be detected among Q2 + Q3, Q2 + Q3 + Q3 R/L, and Q2 + Q3 + Q3 R/C channels (Fig. 2D); the  $V_{1/2}$  (in mV) and  $k$  (in mV/e-fold) values were  $-29.5 \pm 1.1$ ,  $-27 \pm 1.2$ ,  $-30.9 \pm 1.6$ , and  $13.3 \pm 0.5$ ,  $12.5 \pm 0.6$ ,  $11.8 \pm 0.8$ , respectively ( $p > 0.05$ ;  $n = 10$ –15 cells per group). Activation kinetics were also unaffected, as the activation  $\tau$  at 0 mV (in msec) were  $137 \pm 18$ ,  $171 \pm 29$ , and  $136 \pm 23$ , respectively, for Q2 + Q3, Q2 + Q3 + Q3 R/L, and Q2 + Q3 + Q3 R/C channels ( $p > 0.05$ ;  $n = 10$ –15 cells per group).

## DISCUSSION

We report a family with two affected siblings displaying an uncommon clinical course characterized by recurrent seizures beyond the typical age window of BFNS

associated with ID and segregating with a novel *KCNQ3* mutation.

The identification of a *KCNQ3* mutation associated with more severe phenotypes represents a rather novel finding and parallels the emerging data on *KCNQ2*.<sup>3,9</sup> To date, only nine missense *KCNQ3* mutations have been reported in families with early onset epilepsies; seven in BFNS,<sup>5,7,8,10–14</sup> and two in patients with seizure occurrence in the infantile age.<sup>15,16</sup> In most families with *KCNQ3* mutations, affected members showed a benign disease course including age of onset and remission of seizures, sensitivity to AEDs, no recurrence of seizures after the neonatal-infantile period, and normal neurocognitive development. By contrast, in the family described by Soldovieri et al.,<sup>5</sup> febrile seizures beyond the neonatal period and mild to moderate intellectual deficiency occurred in two patients; moreover, an association between infantile seizures and centrotemporal spikes (CTS) on EEG was described by Fusco et al.<sup>16</sup> The presently found mutation (p.R330L) affects the same codon previously reported to be mutated in two BFNS families from different ethnic backgrounds (p.R330C),<sup>7,8</sup> and in an additional BFNS family (p.R330H).<sup>14</sup> The present data reveal that both R330L and R330C Q3 mutations abolished channel function in homomeric configuration, but could be partially rescued in heteromeric channels with Q2 or Q2/Q3 subunits. The degree of functional impairment was significantly greater for R330L than for R330C mutant Q3 subunits, suggesting that the unusual clinical course displayed by the two probands described in the present study may be caused by the underlying specific *KCNQ3* mutation, as described previously for *KCNQ2*.<sup>6,17</sup> Although several mechanisms may account for the mutation-induced reduction in maximal current, the fact that TEA sensitivity is affected by both R330 mutations investigated seems to suggest an impaired incorporation of mutant subunits into functional heteromeric channels. Given the variability in the expression system (*Xenopus* oocytes vs. mammalian cells) and in the experimental setup (not all mutations have been studied in the pathophysiologically relevant 1:0.5:0.5 ratio among Q2:Q3:Q3mut subunits), it is difficult to compare the present functional data with those previously obtained with other *KCNQ3* mutations investigated by electrophysiological experiments. Nevertheless, among Q3 mutations associated with mostly a benign clinical course, although E299K, D305G, and G310V mutations caused a 20–40% reduction in the maximal current of heteromeric Q2/Q3 channels when expressed in *Xenopus* oocytes,<sup>12,18,19</sup> the W309R mutation reduced by >60% channel currents in HEK293 cells, suggesting a dominant-negative effect.<sup>20,21</sup> In our study, a current decrease by about 30% in R330L mutant channels was found, whereas the *I317T* mutation described in two siblings with moderate psychomotor delay reduced heteromeric currents by >60%.<sup>5</sup> Thus, definitive conclusions about potential genotype–phenotype correlations cannot be drawn at this stage.

Notably, our patients showed the typical centrotemporal EEG abnormalities; this age-dependent genetic trait has been previously described in patients with favorable clinical course carrying mutations in *KCNQ2*<sup>22–24</sup> or *KCNQ3*.<sup>16</sup> As the CTS trait is also linked with a wide spectrum of nonepileptic conditions ranging from mild selective performance deficits to complex ID, we hypothesize, as previously suggested,<sup>25</sup> that the coincidence of more traits, either of which has little or no clinical significance alone, may produce substantial clinical effects. In the family herein investigated, the lack of neonatal seizures, considered to be the hallmark of *KCNQ3* pathology, in some individuals may be due to the incomplete penetrance reported in up 10–15% of individuals with BFNS.<sup>26</sup> Although the possible presence of cosegregating genetic factor(s) responsible for the ID and focal seizures cannot be fully excluded in this family at this stage, the variable phenotype observed may be caused by additional genetic, epigenetic, or environmental factors modulating the expressivity of the Q3 R330L mutation; their identification might improve prognostic predictions and genetic counseling.

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## DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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