# First Tunisian case of FGF12-related neonatal epileptic encephalopathy

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## ABSTRACT :

Despite advancements in neonatal care, treatment of neonatal-onset epilepsy is complex and highly challenging. Here, we report the case of a Tunisian newborn whose seizures began at two days of life and whose genetic testing identified a recurrent de novo gain-of-function missense mutation in FGF12 gene (p.R114H in long isoform transcript, p.R52H in the short isoform transcript). The patient showed resistance to multiple antiepileptic treatments but noteworthy lamotrigine, escalated from 2.5 to 25 mg/day, resulted in an initial decrease in seizure frequency. Later the combination of phenobarbital (5 mg/kg) and valproic acid (VPA) (20 mg/kg) reduced the frequency of seizures substantially. At two years of age, the patient showed hypotonia with severe global developmental delay, occasional seizures, and required tube feeding. Our findings underscore the phenotypic variability and therapeutic challenges associated with FGF12-related epilepsy. Early seizure control is imperative for optimizing neurological outcomes in affected individuals, without mentioning the need for advanced research into gene-based treatment strategies

**Keywords:** Neonatal seizures, epilepsy, Fibroblast Growth Factor 12, mutations, therapeutic interventions

## Introduction :

Neonatal seizures are a medical emergency with a diverse range of etiologies and variable outcomes. Despite advancements in neonatal care, pinpointing the underlying causes of seizures in this population remains complex and challenging. Variants in more than 100 genes have been described to be responsible for developmental and epileptic encephalopathy (DEE) [1]. Large gene panels as well as exome sequencing are now the first line in epilepsy genetic testing when they are affordable. Yet the phenotypic spectrum of each gene and often each mutation is large and complex, with no straigthforward therapeutic implications. This report presents the first documented Tunisian case of epileptic encephalopathy linked to an FGF12 mutation, potentially contributing to future discussions on early-onset epilepsy associated with FGF12 hotspot variants

## Case report :

The patient, a boy from non-consanguineous parents with no notable family history, was born by cesarean section at full term, following an uneventful pregnancy without asphyxia. He was hospitalized on the third day of life due to neonatal seizures characterized by spasms and tonic movements. The infant had a clear phenotype with no particular dysmorphic features. Biological and bacteriological tests were negative. The initial electroencephalogram (EEG) was normal, and magnetic resonance imaging (MRI) scans with spectrometric studies showed normal results.

Despite treatment with phenobarbital (PB), seizures persisted. The crises were characterized by hypertonia of all four limbs, fixed gaze, palpebral and perioral segmental myoclonus, frequent hiccups, and sometimes cyanosis with bradycardia. The seizures occurred three to nine times per day and lasted around 2 to 5 minutes each, requiring the use of Phenytoin for the prolonged periods.

In view of the refractory convulsions, additional treatments were introduced, including vitamin B6, Biotin-Thiamine, and folinic acid, but with no improvement. Intravenous clonazepam (CZP) was started on day 20 for recurring seizures, followed by oral Rivotril and Levetiracetam (LEV). An increase in the LEV dose (60 mg/kg/d) was ineffective.

At the age of one month, clinical genetic testing

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with an epilepsy 95-gene panels revealed the presence of a de novo mutation in FGF12 gene: NM_004113.6(FGF12):c.155G>A (p.Arg52His) alias NM_021032.4(FGF12):c.341G>A (p.Arg114His) in the short and the long isoform transcript, respectively. This missense is currently absent in control populations (gnomAD v4) and has been reported several times in patients with very early-onset epileptic encephalopathy, always as de novo variant (#617166; MIM) [4]. Very few pathogenic mutations in FGF12 have been found and R52H/R114H missense is by far the most common mutation. FGF12 encodes an adaptor protein that modulates NaV channels by interacting with their C-terminal cytoplasmic tail [2] and functional characterization in transfected cells demonstrates a gain-of-function for p.R52H/pR114H missense.

A subsequent EEG on day 20 showed a normal background rhythm with paroxysmal anomalies of the spike-wave type, sometimes predominantly centro-temporal and sometimes generalized, with or without clinical manifestations (tonic eye spasm, hypertonia of the limbs) of short duration, indicative of neonatal epilepsy.

Lamotrigine was later used, escalated from 2.5 to 25 mg/day, resulting in an initial decrease in seizure frequency but no complete resolution. Topiramate (TPM) was added but gradually decreased due to ineffectiveness. The combination of PB (5mg/kg) and valproic acid (VPA) (25mg/kg) eventually reduced the frequency of seizures substantially at a rate of one crisis a week.

Unfortunately, the child was lost to follow-up during the coronavirus pandemic and was seen again at the age of two, presenting with occasional seizures. He had hypotonia with severe global developmental delay and poor interaction. He had constipation and feeding difficulties that necessitate tube-feeding.

## Discussion :

Severe neonatal epilepsy syndromes should be considered in neonates without an apparent trigger for acute symptomatic seizures. Genetic testing for epilepsy may offers a clear diagnosis and can guide treatment decisions and prognosis. Recurrent de novo heterozygous missense variant [c.155G>A p.(Arg52His)] of FGF12 has been linked to developmental and epileptic encephalopathy and cerebellar atrophy [1,2]. Functional studies suggest that this gain-of-function variant increases neuronal excitability by altering sodium channel inactivation, leading to severe clinical features, including early-onset intractable seizures, intellectual disability, developmental delay, and cerebellar atrophy [3]. Only a few cases of FGF12-related neonatal epileptic encephalopathy have been reported worldwide, and to our knowledge, this is the first case published in North Africa.

Al-Mehmadi et al. identified three patients with de novo FGF12 mutation [NM_004113.5.155G>A, p.R52H] identical to out patient's. Their salient clinical features were similar including neonatal-onset refractory epilepsy, intellectual disability and severe feeding difficulties. The MRI initially normal at onset, had subsequently shown cerebellar atrophy [4].

Consistent with existing literature, seizures typically present within the first month of life [4,5]. FGF12-related epileptic encephalopathy can present with diverse phenotypes, as demonstrated by our patient, who experienced focal, generalized tonic-clonic, and tonic seizures. This variability is also observed in other studies [2,4].

EEG should ideally be conducted during seizures. In this case, the initial EEG was normal, while the subsequent one revealed multifocal epileptiform discharges. Some patients show a suppression-burst pattern [4]. Brain MRI at seizure onset is often unremarkable, though cerebellar atrophy may develop later [5-6].

FGF12-associated epilepsy is challenging to manage due to high antiepileptic drug resistance rates among affected individuals and their different response to treatment [4-8]. In our patient, seizures control was not achieved with the different antiepileptic drugs. The combination of PB and VPA eventually reduced the frequency of seizures.

To date, the optimal treatment of FGF12 mutation-related epilepsies remains controversial.

Reviewing treatment options for FGF12-related epilepsy reveals limited effective drugs. Good response to PHT was noted in some cases with a partial decrease in seizure activity after treatment [5]. Others studies underscore the effectiveness of high dose PB in FGF12-related neonatal epileptic encephalopathy [6]. PHT and PB pose risks of neurological and behavioral complications and withdrawal issues upon discontinuation [4,7]. Alternative medications have yielded inconsistent results. Recent reports suggest that a combination of VPA and TPM has achieved seizure control in FGF12-related early-onset epileptic encephalopathy [8].

Our findings align with previous literature, highlighting the therapeutic challenges of FGF12-related encephalopathy. This emphasizes the need for refined research into gene-based antiepileptic drug selection and exploration of drug utilization strategies for refractory epilepsy. Early seizure control is crucial for optimizing neurological outcomes.

## Conclusion :

The future of medicine likely lies in leveraging genetic insights to elucidate and address complex pathologies. Technological advancements have positioned genetic testing as a cornerstone in diagnosing early-onset epilepsies that can guide treatment option and greatly enhance patient outcomes. However, further research is needed to fully understand the pathophysiology of FGF12-related encephalopathies and to develop well-defined strategies and targeted therapies.

**Conflict of interest:**
None

## RÉFÉRENCES


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