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LETTER TO THE EDITOR

CLINICAL GENETICS WILEY

*FGF12*p.Gly112Ser variant as a cause of phenytoin/phenobarbital responsive epilepsy

To the Editor:

FGF12 is associated with early infantile epileptic encephalopathy 47 (EIEE47; MIM 617166). Apart from a single patient with gene duplication[1] all 11 reported cases shared the same *FGF12* variant (p.Arg114His/c.341G > A) and responded to phenytoin (PHT) and/or phenobarbital (PB).[2,3]

We present a novel *FGF12* variant, NP_066360.1:p.(Gly112Ser), associated with early-onset epilepsy responding to PHT/PB.

A 4.5-year boy developed normally until 4 months when tonic seizures with decreased saturation and myoclonic seizures appeared. The electroencephalogram (EEG) and magnetic resonance imaging (MRI) were normal. The head circumference was normal and there were no dysmorphic features. At that time PB (5 mg/kg) was successfully used. After 4 months, there was unsuccessful attempt to reduce PB (till 3 mg/kg). At 8 months, proband developed polymorphic seizures—generalized tonic-clonic seizures, episodes with head and eyes rotation and increased muscle tone, myoclonic seizures and later epileptic spasms. Hypotonia with slight asymmetry R > L and preserved tendon reflexes were observed. Regression with seizure onset was evident. Reduced dose of PB had no effect also when combined with clobazam (CBZ) in maximal dose of 0.9 mg/kg, valproic acid (VPA) 37.5 mg/kg, levetiracetam (LEV) 60 mg/kg or vigabatrin (VGB)

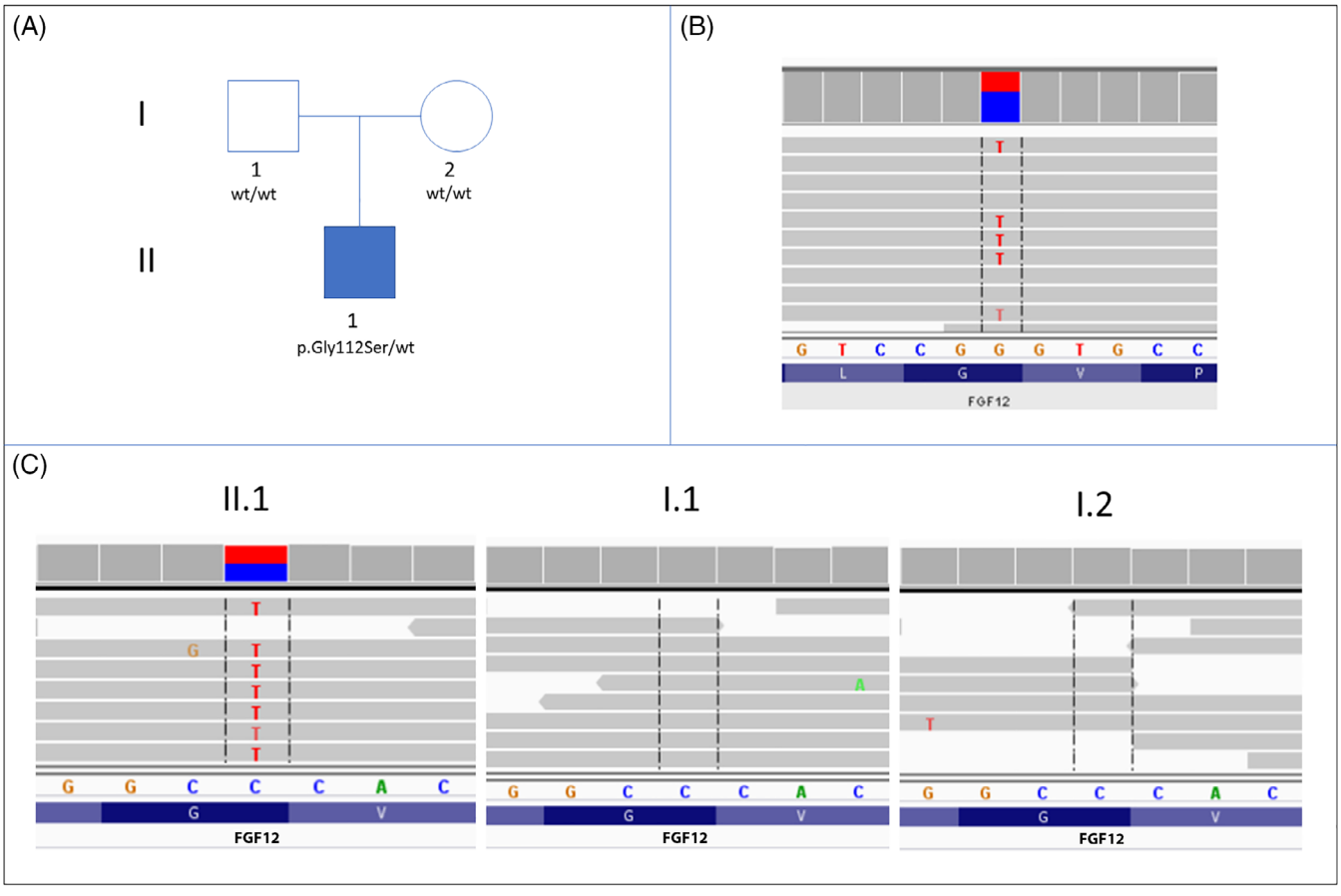

FIGURE 1 A, Family pedigree; B, Integrative Genomics Viewer (IGV) view of whole genome sequencing result in proband; C, IGV view of next-generation sequencing analysis of polymerase chain reaction amplicons spanning the mutation site in proband and his parents confirming *FGF12* p.(Gly112Ser) as de novo [Colour figure can be viewed at wileyonlinelibrary.com]

100 mg/kg. A 2-month long successful steroid treatment was performed but it was complicated by rotavirus infection and hypokalaemia (K-1.8 mmoL/L). Repeated EEG showed generalized (spikes, sharp waves, sharp-and-slow waves complexes, slow waves) and focal paroxysmal changes localized in temporal regions. At 11 months, the muscle tone was strongly decreased with no developmental progress (no roll-over ability) and nasogastric tube dependence. Moreover, autistic features appeared. At 14 months, 4 months after steroid withdrawal, polymorphic seizures reappeared. Ictal video EEG showed generalized polyspikes, spike-slow wave complexes. This time seizures were controlled by combination of PHT (10 mg/kg), PB (5 mg/kg) and LEV (55 mg/kg). At 2.5 years, after 15 months seizure-free period there was an unsuccessful attempt to reduce PB and dosage was increased to 5 mg/kg/day. At 3.5 years, there was another ineffective attempt to decrease PHT dose.

Whole exome sequencing (WES) performed on proband's blood DNA (without trio analysis) showed a heterozygous *FGF12* variant (NM_021032.4:c.334G > A, NP_066360.1:p.(Gly112Ser)) absent from gnomAD database (http://gnomad. broadinstitute.org) and our in-house database (N > 1000). The variant has been predicted as damaging by MutationTaster, FATHMM-MKL, Provean, LRT, SIFT, DANN. Family study based on next-generation sequencing (NGS) analysis of polymerase chain reaction (PCR) amplicons showed that p.(Gly112Ser) resulted from a de novo mutation (Figure 1). Paternity was confirmed with PowerPlex Fusion System (Promega). While our work was in progress p.(Gly112Ser) appeared in ClinVar as likely pathogenic with no additional data.

As a consequence of the identified *FGF12* variant PHT was increased to 15 mg/kg/day which controlled the seizures. At most recent follow-up at 4.5 years, on therapy including PHT (15 mg/kg/day), PB (5 mg/kg/day) and LEV (55 mg/kg/day) proband has been seizure-free and his psychomotor development improved (he was able to walk unsupported) although ataxic and autistic features, hypotonia, poor eye contact as well as no speech were still present.

FGF12 belongs to fibroblast growth factor homologous factor family.[4] These proteins elevate the voltage dependence of neuronal sodium channel fast inactivation by interaction with their cytoplasmic tails. p.Arg114His results in channel gain-of-function which increases neuronal excitability.[4]

It is not clear which medication, PHT or PB, was more effective in our proband. Among reported patients with *FGF12* mutation good response to PHT was observed in three cases, to PB in two.[2,3] Apart from our proband only one patient without seizures received PHT/PB combined therapy. In two other seizure-free cases PB failed.[3]

Whereas the optimal treatment of the *FGF12* associated diseases remains to be determined our report adds evidence of the effectiveness of high-dose PHT and PB.

DATA ACCESSIBILITY

The data that support the findings of this study are available upon request.

ETHICS STATEMENT

The employed procedures were reviewed and approved by the Warsaw Medical University's Ethics Committee. All human subjects participating in the research (or their legal guardians) gave informed consent.

ORCID

Aleksandra Jezela-Stanek https://orcid.org/0000-0001-9814-0324
Rafał Płoski https://orcid.org/0000-0001-6286-5526

Justyna Paprocka,[1] Aleksandra Jezela-Stanek,[2] Agniesz Koppolu,[3,4] Małgorzata Rydzanicz,[3] Joanna Kosińska,[3] Piotr Stawiński,[3] and Rafał Płoski,[3]

[1]*Department of Paediatric Neurology, School of Medicine in Katowice, Medical University of Silesia in Katowice, Katowice, Poland*
[2]*Department of Genetics and Clinical Immunology, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland*
[3]*Department of Medical Genetics, Warsaw Medical University, Warsaw, Poland*
[4]*Postgraduate School of Molecular Medicine, Warsaw Medical University, Warsaw, Poland*

Correspondence
Rafał Ploski, Department of Medical Genetics, Warsaw Medical University, Warsaw, Poland ul. Pawińskiego 3c,02-106 Warsaw.
Email: rploski@wp.pl

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