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CASE REPORT

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A new variant of MYCN gene as a cause of Feingold syndrome

Naim Zeka[1] | **Ramush Bejiqi**[2,3] | **Abdurrahim Gerguri**[1] | **Leonore Zogaj**[1] | **Haki Jashari**[1,4]

[1]Pediatric Clinic, Department of Neurology, University Clinical Center of Kosovo, Pristina, Kosovo

[2]Pediatric Clinic, Department of Cardiology, University Clinical Center of Kosovo, Pristina, Kosovo

[3]Faculty of Medicine, University of Gjakova, Pristina, Kosovo

[4]Pediatric Clinic, University Children's Hospital, Skopje, Republic of North Macedonia

Correspondence
Haki Jashari, Pediatric Clinic, Department of Neurology, University Clinical Center of Kosovo, Lagjja e spitalit, QKUK, 10000 Pristina, Kosovo.
Email: hjashari.md@gmail.com

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Abstract

Feingold syndrome 1 (FS1) is a rare disorder that is inherited in autosomal dominant manner with full penetrance but with variable expressivity. The most common phenotypical features described are finger and toe anomalies, microcephaly, short stature, and intestinal atresia. Dysmorphic features, intellectual disability and other organ anomalies are less frequently described. Here, we present a 7-year-old boy with severe intellectual disability who is diagnosed with FS1 syndrome caused by a new heterozygous variant of MYCN gene

KEYWORDS

digital anomalies, genetic disorder, intellectual disability, microcephaly

1 | INTRODUCTION

Feingold syndrome-1 (FS1) is a rare autosomal dominant disorder. The incidence of FS1 is unknown. However, since 1975 when it was first described by Dr. Murray Feingold,[1] nearly 200 cases are reported up to date. Variable phenotypical features are described, most typical are microcephaly, digital anomalies (short middle phalanxes of the second and fifth finger, syndactyly and hypoplastic thumb), short stature, and intestinal atresias. Additional characteristics include dysmorphic features and intellectual disability. Cardiac and renal anomalies as well as hearing loss are also reported.[2-4] We present here a 7-year-old boy with severe intellectual disability who is diagnosed with FS1 syndrome.

2 | CASE REPORT

We present a seven-year-old male patient who presented to our Pediatric Clinic due to speech delay. He was the first-born child born, normally delivered on term at

40 weeks of gestation. Birthweight was 3350 g, length 44 cm and head circumference 33 cm. His Apgar score was 5 and 7 in 1st and 5th minute, respectively. He was admitted in the neonatal intensive care unit, where supplemental oxygen was given for few days due to respiratory distress. Afterward, the child developed healthy and had no serious illness nor hospitalizations. Physical examination of the child revealed characteristic phenotypical features such as digital anomalies (brachymesophalangy of the second and the fifth fingers clinodactyly of bilateral fifth fingers, hypoplastic thumb), syndactyly of bilateral toes, microcephaly, coarse facial features, micrognathia as well as deformed and relatively large ears (Figures 1 and 2). He weighted 34 kg ($p > 95$), height was 110cm ($p < 1$), and head circumference was 49 cm ($p < 1$).

A specialist in child psychology performed the examination and IQ test, which found the patient to have severe intellectual disability and his IQ to be less than 40 (WISC-IV). The patient was described as very active, showing very little interest for the environment, with very seldom eye contact and also exhibiting stereotyped behavior, for example, rocking. He speaks no word at all, although he utters sounds, sometimes multi-syllable. He does not pay attention enough to the syllables that can be the basis of words. His psycho-motoric development corresponds to 2.5–3 years old.

Neurological examination was performed and there were no signs of laterization, the muscular power was normal, cranial nerves were normal, and pathological reflexes were negative. The patients walk was normal for the age.

The brain MRI was normal. Audiometry shows that hearing was at normal range. Echocardiography and abdominal ultrasound findings were also normal. EEG showed scattered background with multiple focal spikes, polyspikes, and sharp waves (Figure 3), but as the patient did not manifest seizures, no therapy was initiated.

Total serum fatty acid levels showed a low docosahexaenoic acid (DHA) level. Hence, supplementation was started. Metabolic screening and TORCH resulted normal.

In addition, we required the genetic analysis. Exome sequencing analysis of the MYCN gene revealed the heterozygous variant c.1177C>T(p.Arg393Cys), which causes Feingold syndrome type 1. At best of our knowledge, this MYCN variant has not been described in literature before.

As Feingold syndrome is usually inherited in an autosomal dominant manner and rarely represents a de novo mutation, parents of the patients were examined. However, they did not had any dysmorphic features.

3 | DISCUSSION

We have prescribed a patient with severe intellectual disability, microcephaly, digital anomalies (short middle phalanxes of the second and fifth finger and clinodactyly of the bilateral fifth fingers), bilateral toe syndactyly, short stature, and micrognathia. As the patient manifested some of the characteristic features of Feingold syndrome, genetic analysis was conducted which revealed a heterozygous mutation in the MYCN gene. Mutations in the *MYCN* gene cause Feingold syndrome type 1, while mutations in chromosome 13 that delete the *MIR17HG* gene cause type 2. These genes play role in growth and development, particularly before birth.[5-8]

About 60% of patients have a parent that show characteristic phenotype of Feingold syndrome.[9,10] However, the parents of our patient did not show any dysmorphic features; hence, we think that this represents a de novo mutation.

A review published by Celli et al., including all the cases published up to the date, prescribed physical features of 79 patients from 25 families.[3] Brachymesophalangy was the most common feature (95%), followed by microcephaly (86%), toe syndactyly (80%), short palpebral fissures (57%), learning disability (41%), and gastrointestinal atresia (38%). Cardiac and renal anomalies were reported in 14% and 5% of patients, respectively. Hearing loss was reported in 7% of patients.

Additionally, Marcelis et al. complemented the figure of FS1, with 77 more patients, reporting similar figures to Celli et al. regarding physical features. Moreover, short stature was reported in 60% and micrognathia in 32% of

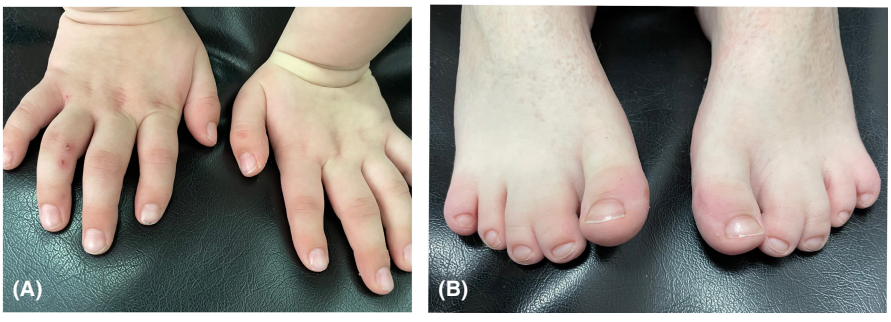

FIGURE 1 Hands and feet of the patient. (a) Digital anomalies, brachymesophalangy of the second and the fifth fingers clinodactyly of fifth fingers, hypoplastic thumbs. (b) Toe syndactyly

patients.[4] Short stature as a feature of FS1 was also described in other studies.[11]

The aforementioned number may lead to the conclusion that the presence of these digital anomalies is essential for a diagnosis of MYCN-related FS. The presence of brachymesophalangy and toe syndactyly in combination with microcephaly and maybe short stature is sufficient to justify MYCN analysis.

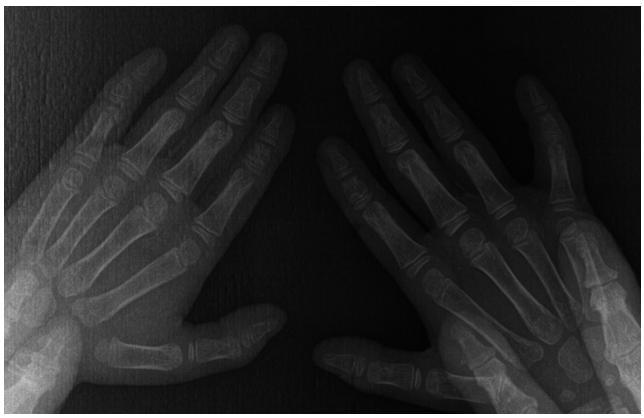

FIGURE 2 X-ray of the hands. Brachymesophalangy of the second and the fifth fingers clinodactyly of fifth fingers, hypoplastic thumbs are shown. Notice the overlapping fingers of the mother, helping the patients to not move his hands

Similar to our case, Chen et al. reported a patient without gastrointestinal atresia, suggesting the MCYN gene mutation might not be sufficient to cause gastrointestinal atresia.[12]

This case report shows that FS1 might present with few anomalies, without intestinal atresia, cardiac and renal anomalies or hearing loss. Having this in consideration, Feingold syndrome frequency might be little higher, but maybe missed. Hence, we recommend that mutational analysis of the MYCN gene should be part of the regular work up in the genetic diagnosis of children with intellectual disability, in association with microcephaly and digital abnormalities, without additional clinical findings important for the phenotype of Feingold syndrome. Moreover, our case presented with severe intellectual disability, not so common in the previous reports, and also, the MYCN variant c.1177C>T (p.Arg393Cys) as a cause of FS1 was not described before. Table 1 shows all the studies published up to date, number of patients included and gene mutation detected.

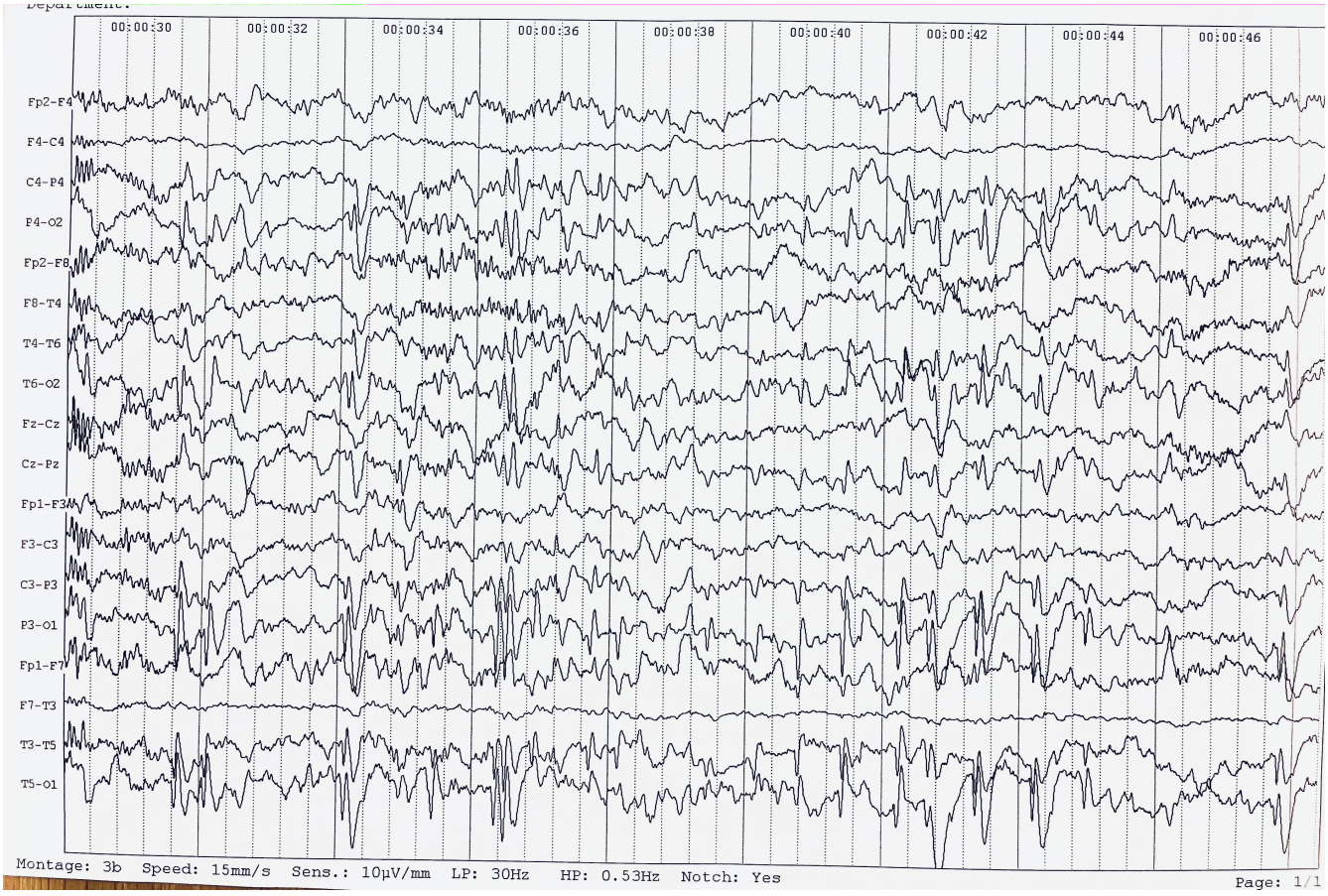

FIGURE 3 EEG of the patient. Scattered background with multiple focal spikes, polyspikes, and sharp waves is seen

TABLE 1 Feingold syndrome type 1 studies, published up to date

Study	Year	Number of Patients	Mutations
Celli[3]	2003	79 (review of 25 families)	Microdeletion of the critical region in 2p23-p24
Marcelis[4]	2008	77	c.134dupC; c.217G>T; c.231G>A; c.302delG; c.451G>T; c.662C>A; c.683delC; c.836_837dup; c.881_882dup; c.915_916insT; c.964C>T; c.1005delC; c.1097dupA; c.1105_1106dup; c.1117C>T; c.1177C>A; c.1178G>A; c.1181G>A; c.1207delA; c.1226C>T; c.1274dupA; c.1293delC; c.1338delA; DelFAM84A_MYCN; DelMYCNOS_MYCN; DelFAM84A_MYCN; DelFAM84A_MYCN_FLJ40869; DelMYCNOS_MYCN
Cognet[13]	2011	17	Eight patients had MYCN mutation c.1180G>A; c.1293delC; c.1110insG; c.928-930insGT; c.474-514del; c.1177C>T; c.134dupC del 2p24.3
Chen[12]	2012	1	Microdeletion of 2p24.3/p24.2 encompassing the genes of FAM84A, NBAS, DDX1, MYCNOS, and MYCN
Burnside[14]	2018	6	Overlapping deletion of (14,614,477–16,148,021) [hg19] including five genes: NBAS, DDX1, MYCNUT, MYCNOS, and MYCN
Klaniewska[15]	2021	5	Variable expressivity of MYCN p.(Ser90GlnfsTer176) mutation
Muirhead[16]	2021	1	Heterozygous missense variants in the POLR3B gene (NM_018082.6), c.1568T>A (p. Val523Glu) and c.2278G>A (p. Ala760Thr); a de novo heterozygous 4-Mb loss of 2p24.3p24.1; and a de novo missense variant in COL2A1 (NM_001844.5), c.1693C>T (p. Arg565Cys)
Tedesco[9]	2021	11 (6 families)	c.503_543del (p. Ala171ArgfsTer81) MYCN gene c.154C>T (p. Gln52X) GNAO1 gene. c.1117C>T (p. Arg373Ter), MCYN gene c.1181G>A (p. Arg394His), MCYN gene
Peleg[17]	2021	1	Novel mutation in the MYCN gene (c.1171C>T; p. Arg391Cys)

AUTHOR CONTRIBUTIONS

Naim Zeka and Haki Jashari contributed to the conception and design of the study. Naim Zeka, Haki Jashari, and Leonore Zeka wrote the manuscript. Ramush Bejiqi and Abdurrahim Gerguri contributed to manuscript revisions, read, and approved the submitted version.

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None.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

ETHICAL APPROVAL

Ethics approval is not required for case studies in accordance with local guidelines.

CONSENT

Written informed consent was obtained from the parents of the patient for publication of the details of their medical case and any accompanying images.

ORCID

Haki Jashari https://orcid.org/0000-0002-4577-8604

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