CASE REPORT

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Kleefstra Syndrome-2 Case with a Novel Mutation and Multiple Disorders

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Abstract

Kleefstra syndrome-2 (KLEFS2) is an extremely rare autosomal dominant condition characterized by a neurodevelopmental disorder and multisystem involvement. The main clinical manifestations include intellectual disability, autistic features, hypotonia, and dysmorphic facial features. We describe a unique case of KLEFS2 in a patient with multiple disorders, treated with anakinra for colchicine-resistant familial Mediterranean fever, who also has delta-beta thalassemia, dyserythropoietic anemia, and butyrylcholinesterase deficiency. A diagnostic dilemma arose because of several abnormalities and distinctive features. This KLEFS2 case exhibited a mild phenotype without neurological deformities. These findings suggest a possible polygenic influence or a convergence of pathways contributing to the complex phenotype. When several abnormalities lead to a diagnostic dilemma, polygenic etiology should be considered.

Keywords: Kleefstra syndrome 2, familial Mediterranean fever, thalassemia, butyrylcholinesterase deficiency

INTRODUCTION

Kleefstra syndrome is a rare autosomal dominant condition mainly characterized by intellectual disability, autistic features, hypotonia and dysmorphic face. Several organs including heart, skelatal and urogenital system may also be affected leading to high phenotypic heterogenity. Hyperactivity, aggressiveness, epilepsy, sleeping disorders, automutilation, insensitivity to pain, abnormal gait, strabismus, hydrocephalus, hypoplasia of cereballar vermis, constipation and dry skin are defined in reported cases. In addition to *euchromatic histone lysine methyltransferase 1* (*EHMT1*) mutations, variants of four more genes have been defined in *MBD5*, *SMARCB1*, *NR1I3*, and *KMT2C*. While there are more than 100 cases of Kleeftsra syndrome-1 (KLEFS1, OMIM:610253) due to *EHMT1* defect that was initially defined in 1999, reported [Kleeftsra syndrome-2 (KLEFS2), OMIM:617786] due to *KMT2C* mutation cases are 130. Although interventions aim to improve behavioral disorders as well as the growth and development of patients, data on long-term prognosis are still lacking.[1-3]

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease endemic in the Mediterranean and the Middle East, causing recurrent attacks of fever and serosal inflammation, and the devastating complication of AA amyloidosis, which can lead to renal failure if left untreated. *MEFV* gene mutations cause dysregulation of the interleukin-1 (IL-1)-mediated inflammatory response, which is successfully controlled by colchicine treatment in the majority of cases.[4]

Thalassemia is a heterogeneous autosomal recessive disorder that is common in the Mediterranean area. Some mutations in the *HBB* gene are inherited in an autosomal dominant manner and lead to a rare form of delta-beta (δ/β) thalassemia that causes mild anemia.[5]

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Autosomal dominant dyserythropoietic anemia type III, on the other hand, is a very rare condition that has been reported in one American and one Swedish family with a unique variant c.2747C>G (p.P916R) in the *KIF23* gene. The following are defined: absent or moderate anemia, hemolysis, multinucleated erythroblasts, and increased risk of monoclonal gammopathy.[6]

Butyrylcholinesterase deficiency caused by *BCHE* mutations is characterized by prolonged postanesthetic apnea. Slow metabolic degradation of choline esters results in prolonged awakening after general or local anesthesia.[7]

We reported a unique case of multiple rare disorders: KLEFS2, FMF, δ/β thalassemia, dyserythropoietic anemia, and butyrylcholinesterase deficiency, presenting with recurrent inflammatory attacks characterized by fever, joint complaints, increased acute-phase reactants, colchicine resistance, behavioral disorders, intellectual disability, a history of anemia, urticarial rash, cervical and mesenteric lymphadenopathy. A diagnostic dilemma arising from several abnormalities and distinctive features led to consideration of a polygenic etiology.

CASE REPORT

A fourteen-year-old female patient has been followed up at our hospital since the age of 9. She presented with dysuria, eye blinking, hand clapping, and insistence on sameness.

She was treated with corticosteroids for hemolytic anemia at four months of age. She was diagnosed with FMF at 16 months of age because of recurrent fever, arthritis, arthralgia, abdominal pain, and elevated acute-phase reactants. Homozygous *MEFV*:p.E148Q mutation was detected, however she did not respond to colchicine. When she was 29 months old, she had minimal hepatosplenomegaly, cervical and axillary lymphadenopathy an urticarial rash, mild intellectual disability, and fever and joint complaints. She had a high hemoglobin F (HbF) level. She was screened in infancy for mutations associated with periodic fever syndromes: mevalonate kinase, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndromes, and deficiency of the IL-1 receptor antagonist and no mutation was detected at another center. IL-1 receptor antagonist Anakinra was also initiated at another center because of persistent fever and elevated acute-phase reactants, which led to an immediate clinical response and normalization of C-reactive protein (CRP) levels. She was also prescribed aripiprazole for behavioral disorders. A mother of advanced maternal age became pregnant after in vitro fertilization treatment. The mother had the thalassemia trait (*HBB*:c.93-21G>A), and the father was healthy; the parents were not consanguineous.

Physical examination revealed short stature (weight at the 3rd percentile; height below the 3rd percentile) with normal pubertal development. She had down-slanting palpebral fissures, a nose with a mild saddle bridge and a bulbous tip, a thin upper lip, a mildly down-turned mouth, misaligned teeth, and a high palate. On psychiatric assessment, she had autism spectrum disorder, with limited social interactions and communication skills, and mild intellectual disability on Wechsler Intelligence Scale for Children-IV. She had a chronic motor tic disorder characterized by eye blinking and stereotypic hand-clapping movements that occurred when she was excited.

Laboratory results revealed leukocyte: 10200/mm^3, 65% lymphocytes, hemoglobine:13 gr/dL, platelet: 417000/mm^3, CRP:0,5 mg/dL, routine urine analysis: 8-10 leukocytes/each area, urine culture: 10^5 colony-forming unit *Escherichia coli*. Lymphocyte predominance was observed, and the lymphocyte panel showed a reversed CD4/CD8 ratio of 0.6. She had a urinary infection. On urinary ultrasound, she had bladder diverticula and bladder wall thickening measuring 5 mm. After treatment of urinary infection with trimethoprim/sulfamethoxazole, voiding cystourethrography was recommended, and voiding education and prophylactic nitrofurantoin were initiated. Bladder wall thickening normalized. Cranial magnetic resonance imaging was normal. A summary of laboratory results is shown in Table 1. Anakinra is continued, and she has normal acute-phase reactants. Aripiprazole is also used in combination with behavioral interventions, which improve but cannot thoroughly correct behavioral problems.

Whole-exome sequencing (WES) was conducted using an Illumina platform with high and uniform coverage (≥20× for 99.65% of targets). Variant detection and annotation were performed using a validated in-house pipeline incorporating VEP v94 and ACMG-based classification. The analysis was limited to a solo WES design without parental sequencing. However, findings and putative carrier status were confirmed by Sanger sequencing in the parents. WES was carried out, with particular focus on Fas mutation and Rett syndrome, both of which were negative. Recently, we detected KLEFS2, δ/β-thalassemia, dyserythropoietic anemia, and butyrylcholinesterase deficiency. WES analysis revealed a *de novo* heterozygous likely pathogenic (PVS1 and PM2) variant (NM_170606.3:c.6652dup; p.(Tyr2218Leufs*18) which is a novel mutation within the *KMT2C* gene. This variant, which causes a frameshift mutation, has not been registered in the NCBI ds database, gnomAD, ESP, 1000 G. Mutations in the *KMT2C* gene are associated with autosomal dominant Kleefstra syndrome type 2 (OMIM®: 617768). Moreover, WES analysis determined potentially relevant variants such as the heterozygous *HBB*:c.93-21G>A mutation causing autosomal dominant δ/β thalassemia/hereditary persistence of fetal hemoglobin (OMIM®: 141749), and the heterozygous *KIF23*:c.2140T>C; p.(Ser714Pro)

Table 1. Laboratory results of the case obtained during febrile attack and attack free periods

Age	8 months	11 years (during febrile atack)	14 years (atack free period)
Leukocyte/mm^3	17300	12140	8100
Hemoglobin (gr/dL)	6	13	12.5
CRP (mg/dL) (n: <0.5)	11.9	6.5	0.23
Erythrocyte sedimentation rate (mm/h) (n: <15)	87	35	14
Serum amyloid a protein (mg/L) (n: 0-7)	N/A	635	5

CRP: C-reactive protein.

causing autosomal dominant congenital dyserythropoietic anemia type IIIA (OMIM®:105600). The carrier status was also detected for a heterozygote likely pathogenic *BCHE*:c.293A>G; p.(Asp98Gly) variation that causes autosomal recessive butyrylcholinesterase deficiency (OMIM®:617936) (Table 2). Familial segregation analysis indicated that the *KMT2C*:c.6652 duplication variant was *de novo,* whereas the *KIF23*:c.2140T>C and *HBB*:c.93-21G>A variants were inherited only maternally. These findings overlapped with the patient's clinical phenotype. Therefore, we assessed putative gene-gene interactions using the publicly available software GeneMANIA (genemania.org) (Figure 1). The results showed that the genes *HBB*, *MEFV*, *KIF23*, and *KMT2C* interacted in the same pathways. Informed consent for publication was obtained from the parents of the case.

DISCUSSION

Kleefstra syndrome is a rare neurodevelopmental disorder with autosomal dominant inheritance. Although both forms of the syndrome are associated with multiple overlapping neurodevelopmental and psychiatric presentations, the clinical features of KLEFS1 and KLEFS2 are presented in Table 3.

Reported patients with KLEFS2 exhibited features including intellectual disability ranging from mild to severe; behavioral disorders (autism, hyperactivity, aggression); mild facial dysmorphisms; short stature; and, rarely, eczema most of which were similar to and present in our defined case.[1,2]

Other features as developmental delay, epilepsy, scoliosis, strabismus, microcephaly, plagiocephaly, recurrent respiratory infections, dry skin, bifid uvula, feeding difficulty, constipation, persistent weight loss, telalgia, hoarseness, inguinal hernia, insensitivity to pain, hydrocephalus, and hypoplasia of cerebellar vermis were differences as not observed in the current case.[1,8,9]

Although hypospadias and cryptorchidism have been reported in the literature, none of the KLEFS2 patients had urological abnormalities; however, the presented case had recurrent urinary tract infections, bladder wall thickening, and bladder diverticula requiring prophylaxis.[1,2] Tic disorders and hand clapping are also present in our patient, whereas they have not been reported in other KLEFS2 cases.

Table 2. Showing whole exome sequencing (WES) results and their characteristics

Gene	Variant	Zygosity	*In silico* parameters*	Allele frequencies**	Type & classification***
KMT2C	NM_170606.3: c.6652dup p.(Tyr2218Leufs*18) rs-	Heterozygous	PolyPhen: - Align-GVGD: N/A SIFT: : N/A MutationTaster: N/A Conservation_nt: N/A Conservation_aa: N/A	gnomAD: - ESP: - 1000 G: -	Frameshift likely pathogenic (class 2) PVS1, PM2,
HBB	NM_000518.4: c.93-21G>A p.? rs35004220	Heterozygous	PolyPhen: - Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation_nt: N/A Conservation_aa: N/A	gnomAD: 0.00015 ESP: 0.00015 1000 G: 0	Effect unknown pathogenic (class 1) PM3, PM2, PP5
KIF23	NM_138555.3: c.2140T>C p.(Ser714Pro) rs-	Heterozygous	PolyPhen: Benign Align-GVGD: C0 SIFT: Tolerated MutationTaster: Disease causing Conservation_nt: moderate Conservation_aa: high	gnomAD: - ESP: - 1000 G: -	Missense uncertain significance (class 3) PM2
BCHE	NM_000055.3: c.293A>G p.(Asp98Gly) rs1799807	Heterozygous	PolyPhen: Possibly damaging Align-GVGD: C65 SIFT: Deleterious MutationTaster: Disease causing Conservation_nt: high Conservation_aa: high	gnomAD: 0.012 ESP: 0.014 1000 G: 0.0060	Missense pathogenic (class 1) PM2, PM1, PP2, PP5

Variant annotation based on OTFA (using VEP v94).
*AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores.
**Genome Aggregation database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G).
***Based on ACMG/ACP recommendations.

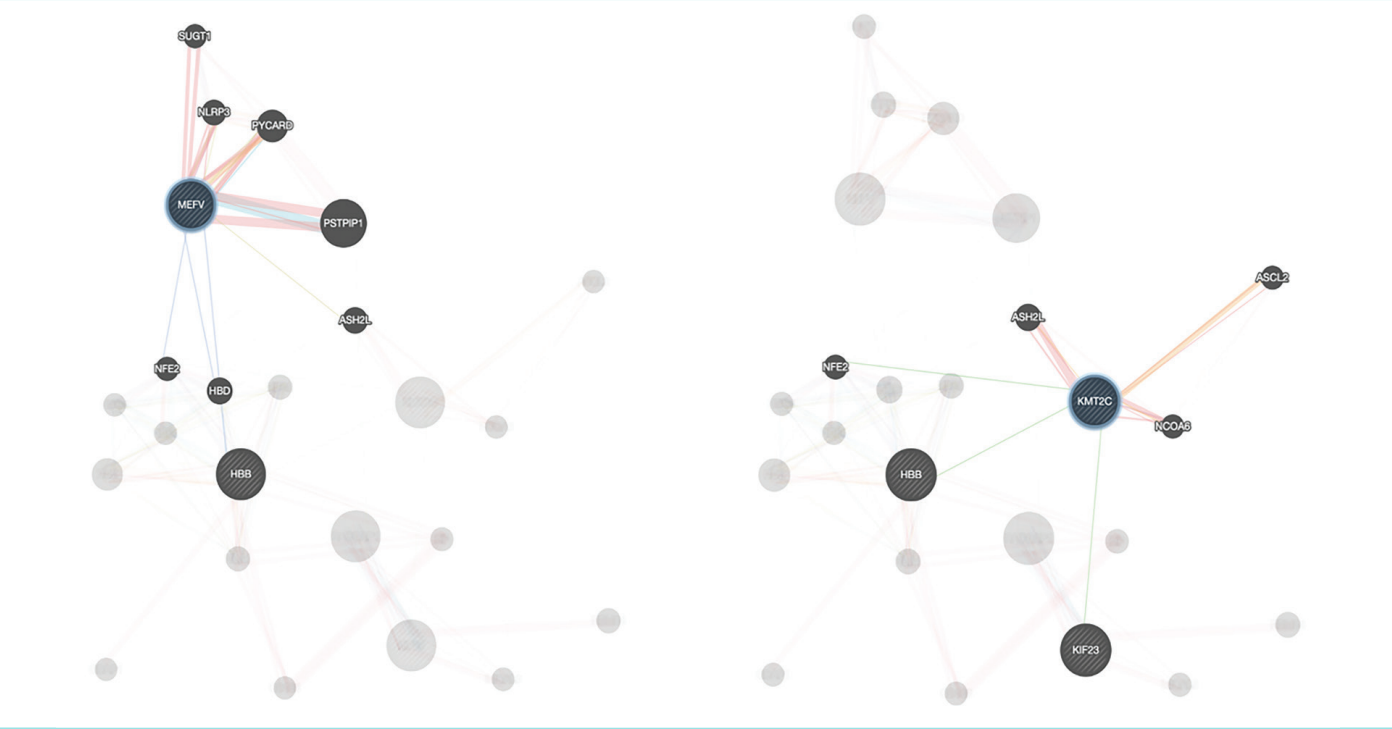

Figure 1. Putative gene-gene interactions of *HBB* and *MEFV* genes and *KIF23*, *HBB* and *KMT2C* interacting in the same pathways.

A 6-year-old female with a *de novo KMT2C* mutation leading to KLEFS2 was reported to have hypotonia, autism, hyperactivity, ventricular gliotic changes, and minor facial anomalies.[2] Another 9-year-old male with a *de novo KMT2C* mutation had developmental delay, anemia in infancy, hyperactivity, scoliosis, and facial features. He was the first case to have eczema, while our case was the second. He also had mild β-thalassemia, which caused anemia in infancy, and our case is the second case of KLEFS2 co-occurring with thalassemia.[1] The current case is distinct for having a rare autosomal dominant δ/β thalassemia and an autosomal dominant dyserythropoietic anemia. She and her mother had a history of anemia during infancy that resolved later in life. Unlike β-thalassemia, anemia is very mild in patients with δ/β-thalassemia. The case had elevated HbF levels, as expected for this disorder.[5] The revealed autosomal dominant dyserythropoietic anemia was also asymptomatic. The detected mutation in the *KIF23* gene is c.2140T>C (S714P), a variant of unknown significance.

Butyrylcholinesterase deficiency is a condition that may cause a prolonged wake-up time after anesthesia. Intellectual disability was also identified in one child, suggesting a connection with *BCHE* mutation. Regulation of dorsal root ganglia and the growth of axons, nerve terminals, and cones were related to *BCHE* in animal experiments. Lower functional *BCHE* activity was also associated with intellectual disability.[7] Investigation of *BHCE* in cancer and pregnancy demonstrated immunological differences in peripheral blood leukocyte populations and an inverse correlation with CD4 and CD8 levels.[10,11] Although the presented case had carrier status for the *BHCE* mutation, the inverse CD4/CD8 ratio may also be attributable to that mutation.

Recurrent inflammatory attacks presenting with fever, arthralgia, increased levels of inflammatory markers, colchicine resistance, behavioral disorders, history of anemia, urticarial rash, cervical and mesenteric lymphadenopathies seemed as FMF with anE148Q mutation was not the only cause, as additional systemic findings led to challenge in diagnosis. Mesenteric lymphadenopathy is described in FMF, but hilar, paratracheal, axillary, pelvic and retroperitoneal lymphadepathies are extremely rare and defined in one case.[12] The inflammatory attacks in the current case were controlled after treatment with anakinra.

Although E148Q mutation of *MEFV* may very rarelycause amyloidosis, renal failure,and death, it should be considered when it is homozygous for timely follow-up and treatment.[13,14] *HBB* and *MEFV*, as well as *KIF23* and *KMT2C* interact in the same genetic pathways; hence, disruptions of these genes likely lead to combined, unexpected phenotypes.

NMDA receptor-dependent neural activity was altered, causing neuronal dysfunction in a mouse model of Kleefstra syndrome; this dysfunction was shown to recover after treatment with NMDA receptor antagonists. NMDAR inhibition also rescued neuronal network phenotypes in mature adults and represents a promising strategy.[15]

Moreover, the upregulation of inflammation-related genes, including IL-1β, which link to immune response, microglial activation and defects was reversed by the neuron-specific lysine methyltransferase G9a-like protein in a mouse model of Kleefstra syndrome. IL-1 receptor antagonist treatment was demonstrated to reverse the neurological phenotypes resulting from haploinsufficiency-induced activation of neuroinflammation via the caspase-1-IL-1β pathway in Kleefstra syndrome. Neurological abnormalities, hypoactivity, and autistic-like features normalized, while the behavioral phenotype was more difficult to correct, suggesting a better outcome with earlier supplementation.[16]

A recent study similarly reported that *KMT2C* mutations cause developmental delay, intellectual disability, behavioral and psychiatric

problems, convulsions, hypotonia, short stature, and facial features. However, they evaluated facial gestalt and deoxyribonucleic acid methylation signatures, suggesting that pathogenic variants in *KMT2C* are different from Kleefstra syndrome, so the condition should be renamed as *KMT2C*-related neurodevelopmental disorder.[17]

A limitation of this study is the lack of functional studies and gene expression analyses to determine the exact effects of alterations in these genes. Whole-genome analysis may be conducted in the future.

Table 3. Clinical features of Kleefstra syndrome variants

KLEFS 1	KLEFS 2
Developmental delay	Developmental delay
Learning difficulties	Small stature
Epilepsy	Hyperactivity
Sleeping disorder	Aggresive behavior
Sleep apnea	Hypotonia
Hearing loss	Autism spectrum disorder
Strabismus	Epilepsy
Hypermetropia	Sleeping disorder
Myopia	Automutilation
Astigmatism	Strabismus
Amblyopia	Cryptorchidism
Glaucoma	Bifid uvula
Cardiac valvular diseases	Inguinal hernia
Atrial fibrillation	Dry skin
Tachycardia	Hoarse voice
Asthma	Delayed puberty
Tracheomalacia	Constipation
Feeding difficulty in infancy	Torticollis
Pes planus	Hydrocephalus
Hypotonia	Hypoplasia of vermis
Scoliosis	Microcephaly
Recurrent infections	Macrocephaly
Hypothyroidism	Brachycephaly
Skin abnormalities	Plagiocephaly
Orofacial cleft	Coarse facies
Congenital kidney/urinary anomalies	Broad and rounded forehead
Behavioral and psychiatric disorders	Deep set eyes
Autism spectrum disorder	Hypertelorism
Anxiety disorder	Down-slanting palpebral fissures
Hyperactivity	Ptosis
Schizophrenia spectrum	Arched eyebrows
Bipolar disorder	Short nose
Depressive disorder	Nose with bulbous tip and saddle bridge
Obsessive-ompulsive trait	Narrow philtrum
Aggressive behavior	Thin upper lip, down-turned mouth
Apathy	Misaligned teeth
Small stature	High palate
Obesity	Preauricular tag
Microcephaly	Duplicated thumb
	Hearing loss
	Scoliosis
	Thoracal kyphosis

KLEFS1: Kleeftsra syndrome-1, KLEFS2 : Kleeftsra syndrome-2.

We presented a unique case with multiple disorders: the first case of Kleefstra syndrome treated with anakinra in which the patient did not have severe mental retardation, epilepsy, or scoliosis. Manipulation of epigenetic regulation has been suggested as a novel therapeutic target for Kleefstra syndrome and warrants further clinical investigation. In addition, this case highlights the possibility of a polygenic etiology and gene-gene interactions in colchicine-resistant FMF, with δ/β-thalassemia-associated *HBB* variation.

CONCLUSION

KLEFS2, a condition with high phenotypic heterogeneity, is a rare cause of neurodevelopmental disorder. Multiple disorders should be considered in atypical manifestations. Genetic testing is required in a timely manner when clinical findings are not clearly evident. Diagnosis is essential for informing prognosis, guiding management and providing genetic counseling in the prenatal or preimplantation setting. Behavioral interventions, with support from family, school, and society, are essential for a long period during the child's growth. Recent approaches may explore early intervention using inflammatory regulators to improve phenotypes.

MAIN POINTS

- Kleefstra syndrome-2 is characterized by a neurodevelopmental disorder with manifestations including intellectual disability, autistic features, hypotonia, and dysmorphic facial features.
- When multiple abnormalities leading to a diagnostic dilemma, a polygenic etiology should be considered.
- Genetic testing is essential when clinical presentation is challenging.

ETHICS

Informed Consent: The authors have written informed consent to publish from study participant's parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.B., Y.E., M.Ç.E., Concept: İ.B., Y.E., M.Ç.E., Design: İ.B., Y.E., M.Ç.E., Data Collection and/or Processing: İ.B., Y.E., M.Ç.E., Analysis and/or Interpretation: İ.B., Y.E., M.Ç.E., Literature Search: İ.B., Writing: İ.B.

DISCLOSURES

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