PERINATAL JOURNAL

Original Article

Perinatal Journal 2025; 33(2):107-115

https://doi.org/10.57239/prn.25.03320013

Complex genetic interactions in a Jordanian pediatric patient with a rare oligogenic disorder: A case report

Fawzi Irshaid Irshaid[1*], Mariam A. Abu-Al-Basal[2], Rana Ahmad Almuhur[1], Alia Khwaldeh[3]

[1]*Department of Biological Sciences, Faculty of Science, Al al-Bayt University, P.O.BOX 130040, Al-Mafraq 25113, Jordan*
[2]*Department of Medical Laboratory Science, Faculty of Applied Medical Sciences, Al al-Bayt University, P.O.BOX 130040, Al-Mafraq 25113, Jordan*
[3]*Department of Allied Medical Sciences, Jadara University, P.O.BOX 733, Irbid 21110, Jordan*

Abstract

We present a case of a 6-year-old Jordanian male patient with intrauterine growth retardation, fine and gross motor delay, recurrent infections, respiratory and gastrointestinal problems, immunodeficiency, and distinctive dermatological abnormalities. Comprehensive genetic evaluation identified a homozygous pathogenic variant in the cystatin A gene (c.64A>T; p. Lys22Ter), consistent with a diagnosis of acral peeling skin syndrome. Furthermore, two variants of uncertain significance were identified in BACH2 (c.100G>A; p. Asp34Asn, heterozygous) and NSMCE3 (c.877G>A; p. Ala293Thr, homozygous). These two genes may contribute to the patient's immunodeficiency and genomic stability. The patient was also a heterozygous carrier of pathogenic variants in the MEFV gene (c.2230G>T; p. Ala744Ser) linked to familial Mediterranean fever. Carrier status was also noted for the phenylalanine hydroxylase gene (c.157C>T; p. Arg53Cys). This gene is linked to phenylketonuria. To the best of our knowledge, this is the first case study that was confirmed by clinical, biochemical, and molecular genetic findings in Jordan. This case underscores the utility of comprehensive genomic analysis in accurately diagnosing complex genetic disorders and highlights the necessity of phenotypic correlation in variant interpretation and future patient management.

Keywords: Chronic diarrhea, Growth retardation, Homozygous pathogenic, Immunodeficiency, Variant rare genetic diseases.

Introduction

Rare genetic diseases are clinically heterogeneous conditions that individually affect a small fraction of the population. Rare genetic diseases are characterized by a prevalence of ≤1 in 2,000 individuals, and often less than 1 in 2,000 people [1]. Due to underdiagnoses and lack of registries, exact prevalence remains uncertain, but estimates suggest that these disorders influence nearly around 400 million people worldwide, underscoring their cumulative public health significance [2]. Most importantly, numerous rare genetic diseases manifest in childhood, with severe cases leading to early mortality [3]. Among these, Acral Peeling Skin Syndrome (APSS) is an uncommon autosomal recessive condition marked by painless shedding of the top layer of the skin on hands and feet and frequently induced by mechanical injury [4]. The condition is most frequently associated with biallelic pathogenic variants in the cystatin A (CSTA) gene, which encodes cystatin A.

A second example of a rare genetic disease is the Familial Mediterranean Fever (FMF). It is a hereditary autoinflammatory condition transmitted in an autosomal recessive manner [5]. It mainly affects populations in the Mediterranean and the Middle East, including Arabs, with symptoms frequently appearing during childhood. It is marked by repeated or recurrent episodes of fever accompanied by serosal inflammation [6]. The third example is phenylketonuria (PKU). It is a rare autosomal recessive metabolic disorder due to pathogenic mutations in the Phenylalanine Hydroxylase (PAH) gene [7]. A deficiency or total lack of PAH usually results in increased phenylalanine levels because of disrupted phenylalanine metabolism, leading to various clinical manifestations, including impaired growth, severe neurological dysfunction, intellectual disability, and cognitive deficits [8].

Taken collectively, genetic disorders with multisystem involvement pose diagnostic challenges due to overlapping clinical features and phenotypic variability. Additionally, the heterogeneous nature of rare genetic diseases, early onset, and frequent diagnostic challenges necessitate advanced genomic approaches. Whole Exome Sequencing (WES) has emerged as a powerful diagnostic tool for unraveling complex genetic phenotypes, especially in pediatric

Correspondence: Fawzi Irshaid Irshaid, Department of Biological Sciences, Faculty of Science, Al al-Bayt University, P.O.BOX 130040, Al-Mafraq 25113, Jordan, **e-mail:** irshaid@aabu.edu.jo, **Received:** August 16, 2025 **Accepted:** October 1, 2025

cases with multisystem manifestations. Herein, we describe the clinical and laboratory features of a unique pediatric patient. A thorough genetic analysis revealed the presence of two homozygous pathogenic variants, one in the CSTA gene and the other in the Non-Structural Maintenance of Chromosomes Element 3 (NSMCE3) gene. Additionally, three heterozygous variants were identified, comprising the BTB Domain and CNC Homolog 2 (BACH2), MEFV, and PAH genes.

Case report

This case study describes a 6-year-old Jordanian boy who experienced upper respiratory and gastrointestinal infections. The patient was taken into a private children's clinic in Irbid, Jordan, where he received additional assessment, diagnosis, and care. At 32 weeks gestation, the fetus was diagnosed with intrauterine growth retardation. At birth, the infant was delivered at full term (40 weeks), despite being small for his gestational age, according to his medical records (Table 1). Upon examination, the patient also exhibited failure to thrive and hearing abnormality. Subsequently, his postnatal course has been complicated by chronic cough, fever, and frequent upper respiratory tract infections. Other clinical symptoms include recurrent infection and digestive problems such as frequent gastrointestinal infection, abdominal pain, chronic diarrhea, and steatorrhea. Dermatologic assessment revealed dermatological abnormalities such as dark skin folds in areas like the neck and underarms (armpits) as well as in the elbows and groin area. The dermatologic examinations also showed a limited, sporadic, painless skin peeling on the hands and feet. Furthermore, neuromuscular analyses revealed that our patient exhibited fine and gross motor delay, including exercise intolerance, displayed tip-toe walking, and experienced easy fatigability. Immunologic evaluation demonstrated a low immunoglobulin IgA level (hypogammaglobuline mia), consistent with a primary immunodeficiency. Moreover, hematological assessment demonstrated microcytic hypochromic anemia, thrombocytosis, low hemoglobin, low mean corpuscular volume, low mean corpuscular hemoglobin, high platelets, high red cell distribution width, and high lymphocytes.

The patient was born to consanguineous parents, which increases the risk of homozygosity for harmful recessive alleles and, hence, genetic diseases. In order to determine possible underlying genetic etiologies, a thorough genetic investigation was conducted due to the multisystemic involvement and the complexity of the clinical presentation. This assessment included mitochondrial genome sequencing, deletion and duplication analyses, and Whole-Exome Sequencing (WES) (Table 2). Additionally, to determine allele frequencies, inheritance pattern, pathogenicity and associated diseases, the identified genetic variants were analyzed using population and clinical databases, including American College of Medical Genetics and genomics (ACMG) guidelines, the genome aggregation database (gnomAD), the Human Gene Mutation Database (HGMD), Rare Exome Variant Ensemble Learner (REVEL) and ClinVar. Variant frequency within these datasets is crucial for the process of variant interpretation as well as could help to assess the potential impact of these variants on human health. High-frequency variants are often viewed as polymorphisms with restricted clinical relevance, whereas rare or novel variants might warrant further investigation to explore potential association with disease phenotypes.

Genetic analysis of the patient revealed a homozygous nonsense variant in the CSTA gene (c.64A>T; p.Lys22Ter), which had previously been classified as pathogenic in individuals with autosomal recessive Papillon-Lefèvre syndrome (APSS; OMIM #184600). In addition, two variants of uncertain significance (VUS) were identified: a heterozygous missense variant in BACH2 (c.100G>A; p.Asp34Asn) and a homozygous missense variant in NSMCE3 (c.877G>A; p.Ala293Thr). A heterozygous missense variant in BACH2 is implicated in BACH2-related immunodeficiency and autoimmunity (OMIM # 605394). On the other hand, a homozygous missense mutation in NSMCE3 can cause chromosome breakage syndrome with immunodeficiency (OMIM #608243), a rare genetic disorder marked by early-onset acute respiratory distress syndrome and genomic instability.

Furthermore, our patient was found to be a carrier of a MEFV gene variant (c.2230G>T; p.Ala744Ser), which is linked to FMF and acute febrile neutrophilic dermatosis (OMIM #608107). Notably, a heterozygous missense mutation in the PAH gene (c.157C>T; p.Arg53Cys) linked to phenylketonuria (PKU; OMIM #612349) was also discovered in our

patient. It is important to highlight that the genetic analysis of genomic DNA derived from our case study found no clinically relevant Copy Number Variations (CNVs) related with the reported disease.

For a patient presenting with multisystemic manifestations, a comprehensive multidisciplinary approach is essential to ensure optimal management and care. This approach should encompass the coordinated efforts of clinical physicians, nurses, dietitians, genetic counselors, pediatricians, physical therapists, and other relevant healthcare professionals. Our patient may benefit from careful calorie management in order to maintain optimal growth and health. Furthermore, depending on the exact types of gene mutations present, enzyme replacement treatment and vitamin supplements (e.g., A, D, E, and K) can help to alleviate some symptoms. Preventive healthcare treatments, such as routine immunizations and the annual influenza vaccine (where eligible), are strongly advised for our patient to lower the risk of infections and consequences. Adherence to these therapies, including home therapies, as prescribed, is critical to our patient's overall health and longevity.

Table 1. Clinical manifestations of a six-year-old male patient from Jordan

Parameter	Clinical manifestations
Gestational age and birth weight	40 weeks and 2350 grams (Small for gestational age)
Hearing manifestation	Hearing abnormality
Growth manifestation	Failure to thrive
Neuromuscular manifestations	Delayed motor milestones, exercise intolerance, displays tip-toe walking and easy fatigability
Immunological manifestations	Increased infection susceptibility, inflammation and hypogammaglobulinemia
Dermatological manifestations	Dark skin folds in areas and sporadic painless skin peeling on the hands and feet
Respiratory problems	Chronic cough, fever and frequent upper respiratory tract
Gastrointestinal problems	Frequent gastrointestinal infections, abdominal pain, steatorrhea and chronic diarrhea
Homological manifestations	Microcytic hypochromic anemia, thrombocytosis, low hemoglobin, low mean corpuscular volume, low mean corpuscular hemoglobin, high platelet, high red cell distribution width and high lymphocyte.

Table 2. Molecular characterization of identified genetic variants, including classification, genomic and proteomic changes, inheritance patterns and associated disorders in patient case study

Classification	Gene	Genomic Location	Exon	DNA Change	Protein Change	Zygosity	IP	OMIM	Associated Disease
Pathogenic	CSTA	Chr3:122044203-122044203	1	c.64A>T	p.Lys22Ter	HO	AR	184600	APSS
US	NSMCE3	Chr15:29561033-29561033	1	c.877G>A	p.Ala293Thr	HO	AR	608243	LD, ID, CBS
US	BACH2	Chr6:90718464-90718464	6	c.100G>A	p.Asp34Asn	HE	AD	605394	ID, AI
Pathogenic	MEFV	Chr16:3293257-3293257	10	c.2230G>T	p.Ala744Ser	HE	AR, AD	608107	FMF, AFND
Likely Pathogenic	PAH	Chr12:103306580-103306580	2	c.157C>T	p.Arg53Cys	HE	AR	612349	PKU

US: Uncertain Significance; HO: Homozygous; HE: Heterozygous; IP: Inheritance Pattern; AR: Autosomal Recessive; AD: Autosomal Dominant; ID-60: Immunodeficiency 60; AI: autoimmunity; APSS: Acral Peeling Skin Syndrome, LD: Lung Disease; CBS: Chromosome Breakage Syndrome; FMF: Familial Mediterranean Fever; AFND: Acute Febrile Neutrophilic Dermatosis; PKU: Phenylketonuria

Discussion

Our patient is a 6-year-old child with consanguineous parents. He exhibited multiple immunological and hematological abnormalities, neuromuscular dysfunctions, dermatological manifestations, and recurrent infections of the respiratory and gastrointestinal tracts, accompanied by systemic symptoms. As a result, our patient may be more vulnerable to genetic diseases because they are more likely to inherit the same recessive gene mutations from both parents, which increases the likelihood that our patient will develop inherited conditions. These findings prompted us to investigate potential underlying genetic causes through a comprehensive genetic analysis, in particular WES. Indeed, the genetic investigation revealed that our patient possessed a relatively small number of genetic abnormalities or mutations associated with the complicated clinical phenotype detailed in this case report.

Interestingly, a homozygous nonsense mutation in the CSTA gene (c.64A>T; p.Lys22Ter) was identified by WES analyses. The CSTA is a variant previously reported as pathogenic and causative of APSS (OMIM #184600) [4]. APSS is a rare autosomal recessive genodermatosis that can be characterized by superficial epidermal peeling, primarily localized to the acral regions of the distal extremities (i.e., the hands and feet). It has been found that the CSTA gene encodes cystatin A, an epidermal cysteine protease inhibitor essential for maintaining skin or epidermal integrity by regulating lysosomal proteolytic activity within keratinocytes. In fact, the identified nonsense mutation introduces a premature stop codon in the resulting mRNA transcript of CSTA mRNA. This nonsense variant can cause mRNA decay or the production of a truncated protein, leading to the complete or partial loss of cystatin A function [9]. This disrupts the inhibition of epidermal cysteine proteases like cathepsins B and L, allowing unchecked proteolytic activity within the epidermis, especially in acral regions. This unregulated proteolysis thereby results in defective cell-cell cohesion and skin fragility, leading to the characteristic painless desquamation observed in the APSS phenotype. In addition to its skin manifestations, emerging evidence suggests that certain CSTA mutations may present with systemic features, although these associations remain poorly defined. The symptoms seen in this case study align with the well-defined APSS phenotypic manifestations reported in previous publications [4, 9]. Collectively, the discovery of a homozygous nonsense mutation in the CSTA gene offers compelling evidence for its connection to skin abnormalities and corresponds with the well-known phenotype of APSS. This finding may also warrant further investigation into interacting pathways, such as inflammatory cascades or additional protease inhibitors (e.g., SERPIN family genes).

Furthermore, our patient exhibited reduced serum IgA levels, microcytic hypochromic anemia, thrombocytosis, and frequent respiratory and gastrointestinal infections, suggesting immune dysfunction. These findings also indicated the involvement of additional genetic modifiers, oligogenic factors, or a complex genetic background. Interestingly, a homozygous missense variant in the NSMCE3 gene (c.877G>A, p.Ala293Thr) was detected in our patient. A missense mutation in this gene is linked to autosomal recessive chromosomal breakage syndrome as well as implicated in lung disease immunodeficiency (OMIM #608243). As noted by Karczewski et al. (2020), the African/African-American group shows the greatest allele population frequency (0.07%) in gnomAD, followed by the entire population at 0.007% [10]. As far as we know, this variant has not been identified as a disease-causing variant in the literature. REVEL, or *in silico* meta-analysis, indicates a tolerated effect on protein function [11]. Moreover, there is presently inadequate evidence to ascertain the pathogenicity of this variant. As a result, the NSMCE3 variant (c.877G>A, p.Ala293Thr) is currently categorized as a variant of uncertain significance.

According to a prior study, mutations in NSMCE2 or NSMCE3 were identified in patients with primordial dwarfism, severe insulin resistance, gonadal failure, chromosome breakage syndrome, fatal pulmonary disease in early childhood, and immunodeficiency [12]. Recent studies reported that NSMCE3 is a component of the SMC5/6 complex. In addition, homozygous mutations of NSMCE3 lead to impaired SMC5/6 complex stability, resulting in chromosomal instability and disruption in homologous recombination [13]. These disruptions lead to

impairing T and B cell function and may exacerbate immunodeficiency, causing early-onset acute respiratory distress syndrome. These clinical manifestations are consistent with immunologic and hematological findings in our patients, supporting the role of homozygous missense mutation in the NSMCE3 gene.

The current case study additionally indicated that our patient exhibited a heterozygous missense mutation in BACH2 (c.100G>A, p.Asp34Asn), which has been linked to immunodeficiency (OMIM #605394). The heterozygous p.Asp34Asn mutant found in our case appears to be a rare alteration in the BACH2 gene. Besides, REVEL, or in silico predictive tools, provides inconclusive results regarding the impact of this BACH2 variant on protein function. Owing to a lack of adequate evidence, this variant is currently classified as a variant of uncertain significance. It is crucial to note that this gene encodes a transcriptional regulator that is essential for the function of regulatory T cells as well as the maturation and differentiation of B lymphocytes. Afzali et al. (2017) describe a syndrome of BACH2-related immunodeficiency and autoimmunity due to BACH2 haploinsufficiency, resulting in lymphocyte maturation defects, hypogammaglobulinemia, and intestinal inflammation [14]. The authors found that haploinsufficiency affected protein stability by interfering with homodimerization or inducing aggregation. Prior studies revealed that variants in BACH2 are found in patients with immune dysregulation syndromes and autoimmunity diseases like systemic lupus erythematosus, type one diabetes, Addison's, and Graves' disease [15, 16]. In addition, recently Van Konijnenburg and his team (2023) found a link between BACH2 mutations and the development of hypogammaglobulinemia [17]. This immunoglobulin deficiency was believed to predispose affected patients to recurring and chronic infections, specifically those affecting the respiratory and gastrointestinal systems. These clinical features align with our findings in our patient. While rare genetic disorders such as cystic fibrosis and systemic autoimmune diseases (e.g., systemic sclerosis and systemic lupus erythematosus) could be considered, they were excluded owing to the absence of characteristic clinical features in this case. Most importantly, our findings add to the expanding body of data that the autosomal dominant BACH2 variant leads to pathogenesis of immunodeficiency, raising the possibility of partial phenotypic expression in our case study.

Although genotype–phenotype predictions are theoretically achievable, their precision is often compromised by biological complexities like genetic redundancy, epistatic interactions (gene–gene effects), and gene-environment interactions [18]. Consequently, the implications of identified gene–gene interactions need to be carefully interpreted in conjunction with our patient's clinical symptoms and biochemical profile. In our case, the clinical manifestations suggest a genotype-phenotype connection involving BACH2 and NSMCE3, both of which have been associated with immunodeficiency syndromes. These findings highlight their potential roles in modulating immune dysfunction and underscore the influence of functional redundancy among immune-related genes on disease expression and severity. The coexistence of these two variants may enhance the likelihood of synergistic interactions between them. Despite the fact that mutations in BACH2 and NSMCE3 remain poorly understood, their coexistence warrants further investigation into their potential molecular interplay and shared pathways in autoimmunity. Focused investigations of these genes may provide additional insights into their pathogenic interpretation and advance our understanding of their contributions to immune dysregulation as well as to their genotype-phenotype associations.

Interestingly, genetic analysis identified a third distinct genetic finding in our patient, consisting of heterozygous variants in both the MEFV and PAH genes. Our patient was a heterozygous carrier of pathogenic variants in MEFV (c.2230G>T, p.Ala744Ser) that usually link to FMF and acute febrile neutrophilic dermatosis (Sweet syndrome). In this case, the identified mutation in the MEFV gene was classified as pathogenic, exhibiting either an autosomal recessive or autosomal dominant pattern of inheritance. A prior study done by Rowczenio et al. (2017) revealed that FMF is primarily confirmed in most cases via identifying genetic mutations in the MEFV gene [19]. The carrier rate of the MEFV gene could be as high as 1:3 in some regions. The gene encodes the pyrin protein, which is crucial for controlling inflammation and is regarded as a negative regulator of inflammation. Besides, MEFV

gene mutations generally linked to autosomal recessive FMF. The primary signs of MEFV disorders include recurrent fever and inflammation of the serosa impacting the joints, chest, and abdomen. Skin rashes and digestive problems are often present as well. Later, Mezher et al. (2024) reported that numerous patients have a single MEFV mutation, with some heterozygotes exhibiting symptoms comparable to homozygotes, suggesting a variable penetrance dominant inheritance pattern [20]. Homozygotes often show more intense symptoms, indicating a dose-dependent influence. Pseudo-dominant inheritance occurs in populations with high allele frequency and consanguinity. Recently, Feghali et al. (2025) and Mertz et al. (2025) presented evidence that certain heterozygous patients with MEFV gene mutations may exhibit mild autoinflammatory symptoms [6, 21]. These mutations are marked by innate immune system dysfunction and recurrent episodes of systemic inflammation without involvement of high-titer autoantibodies or antigen-specific T cell responses.

In addition, Sweet syndrome is a very rare skin disorder marked by erythematous plaques and red-to-purple papules and fever. This syndrome is associated with a variety of illnesses, including upper respiratory tract and gastrointestinal system diseases, cancer and inflammatory bowel disease (Crohn disease and ulcerative colitis), autoimmune disorders, and others [22]. Recently, Mertz and colleagues reviewed the role of pyrin in regulating the immune response and highlighted its involvement in FMF and pyrinopathies [6]. These conditions are associated with dominantly inherited pathogenic mutations in the MEFV gene, leading to autoinflammation characterized by acute febrile neutrophilic dermatosis, hypereosinophilia, and neuroinflammation. Therefore, the MEFV variant detected may contribute to subclinical inflammation or mild autoinflammatory symptoms, suggesting partial phenotypic expression in our studied case. These observed inheritance patterns indicated that the identified MEFV variant may have an autosomal dominant mode of transmission.

In this study, the PAH gene variant c.157C>T (p.Arg53Cys) was identified as likely pathogenic using current variant interpretation guidelines. This gene encodes phenylalanine hydroxylase, crucial for converting phenylalanine into tyrosine through hydroxylation. The PAH gene encodes PAH, and a lack of this enzyme leads to PKU, a genetic metabolic disorder marked by disrupted phenylalanine catabolism. A deficiency or functional impairment in PAH activity results in phenylalanine buildup in the body, leading to toxic levels in the blood and brain tissues [23]. Patients with PKU may have significant developmental delays and irreversible intellectual disabilities. They may also exhibit development failure, hypopigmentation, motor impairments, ataxia, microcephaly, and severe neurological impairments. Recent studies reported that individuals with clinical PKU often have homozygous or compound heterozygous mutations in the PAH gene, which causes a deficit of the PAH [7, 8]. Moreover, several point mutations in the PAH gene are recognized as responsible for PKU across different ethnicities, while significant deletions or duplications represent up to 3% of the PAH mutations within certain ethnic populations [8, 23]. Consequently, these results suggest that heterozygous PAH variants, such as PAH c.157C>T, do not play a role in the phenotype observed in our case study, highlighting the primary influence of homozygous PAH variants in the development of PKU. Nevertheless, because of its potential phenotypic effects, ongoing clinical monitoring and individualized treatment approaches are still required to enhance patient outcomes.

Kingdom and Wright (2022) revealed that a single genetic variant can lead to diverse phenotypes, ranging from asymptomatic to severe, due to incomplete penetrance and variable expressivity [24]. These clinical variabilities are influenced by epigenetic changes, genetic modifiers, inheritance patterns, and environmental factors. Additionally, it is still early to judge the phenotypic effects of these variants in our patients, since our patient is 6 years old. This is because some variants may express or manifest their phenotypic effects later in life. Moreover, heterozygous carriers of pathogenic or likely pathogenic variants in autosomal recessive disorders are generally considered asymptomatic. However, recent investigations present new findings indicating that mild and non-specific symptom expressions can emerge in some heterozygote individuals later in their life, generally manifesting as less severe than in those with biallelic mutations. These symptoms were recognized in several disease categories,

especially in neurological, hematological, pulmonary, and neuromuscular disorders [25, 26]. These findings suggest that this symptomatic heterozygosity undermines the classical Mendelian inheritance model by demonstrating that people with a single harmful allele can have moderate symptoms similar to dominant illnesses. Thus, symptomatic heterozygosity remains a complex and understudied topic that highlights the limitations in a binary dominant/recessive paradigm, despite its growing recognition. Most crucial, the molecular basis of the paradigm necessitates more explanation and further elucidation via several studies at the genetic and protein levels. These functional studies can also focus on elucidating the molecular mechanisms operating within intricate genetic environments and improve personalized management and therapy. Nonetheless, addressing these issues and difficulties extends or goes beyond the scope of this case report, emphasizing the need for further investigation.

Interestingly, the broad clinical manifestations observed suggest heterozygous mutations may have wider phenotypic effects than previously recognized. It is also unclear whether similar clinical and genetic profiles could exist in populations within or beyond Jordan. Thus, this case demonstrates the challenges in interpreting heterozygous mutations within complex genotype-phenotype relationships, warranting reassessment of their inheritance patterns. Besides, the functional and pathogenic roles of these heterozygous variants remain uncertain. To address these uncertainties, future studies should prioritize functional characterization of these variants and their interactions with genetic and environmental modifiers. These future studies will help clarify their pathogenic mechanisms, potential synergism, and contribution to the observed clinical heterogeneity. Finally, yet importantly, our diagnostic approach employed, based on WES, has limitations, including its inability to detect certain pathogenic mutations like deep intronic, splicing, or other overlooked variants. Without comprehensive molecular research, including whole-genome sequencing and functional testing, it is difficult to determine whether these alleles are recessive or dominant.

Conclusion

In conclusion, this unique report details a rare case of a 6-year-old male patient experiencing multisystem dysfunctions, affecting the neuromuscular, respiratory, gastrointestinal, and immune systems and skin. Besides, five pathogenic or likely variants were identified, comprising the CSTA, NSMCE, BACH2, MEFV, and PAH genes. These findings support an oligogenic inheritance model in our case, leading to key questions about how these variants interact, their inheritance patterns, and their clinical significance. Besides, the wide spectrum of manifestations and complexity of the genetic interaction render interpretations and conclusions quite challenging or difficult. Therefore, the specific roles of these variants in shaping the observed multisystem phenotype require further elucidation.

Given the patient's young age, the long-term impact of these variants in our patients may not yet be fully apparent. Therefore, this case highlights the necessity for continued follow-up, broader comparisons, and functional studies to elucidate the pathogenesis and phenotypic variability of these mutations. Given the clinical implications, comprehensive screening of the five candidate genes and further research on modifier genes are essential. This case study also highlights the challenges in early diagnosis for patients and biologically relevant relatives, as well as the necessity for individualized therapies.

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