Full Length Research Article

A Case Report of X-Linked Hyper-IgM Syndrome Associated with the CD40LG Variant: Successful Management with Immunoglobulin G Replacement Therapy

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ABSTRACT

Background: X- linked hyper- IgM syndrome (X- HIGM) is a rare primary immunodeficiency disorder characterized by recurrent infections, hypogammaglobulinemia, and elevated IgM levels. The condition results from mutations in the *CD40LG* gene, which encodes CD40 ligand, a protein essential for B cell activation and immunoglobulin class switching. This study presents a clinical case of X-HIGM in a young child and highlights the effectiveness of immunoglobulin G replacement therapy in managing the disease.

Methods: Whole-exome sequencing and Sanger sequencing were performed to identify the genetic cause of the patient's recurrent infections. A hemizygous c.409+1_409+19del mutation was identified in the *CD40LG* gene, confirming the diagnosis of X-HIGM. Immunoglobulin G replacement therapy was administered to manage the patient's condition.

Result: Peripheral immunoglobulins confirmed the clinical observations, with low IgG and A but strikingly high IgM levels. Recurrent otitis media and pneumonia were common in early childhood. The genetic testing performed afterward confirmed that the mutation was present in the two affected siblings. This favorable clinical response with a decrease in the frequency of infections and the stability of the IgG levels over the time suggests that IgRT may have a long- term effective role in the management of a rare primary immunodeficiency. It also stresses the need for genetic workup for diagnosis, family counselling, and management of rare immunodeficiency syndromes.

Conclusion: This case highlights the need for early diagnosis and treatment of X- HIGM. IgG replacement therapy is an effective option when stem cell transplantation is not possible or suitable.

INTRODUCTION

X-linked hyper-IgM syndrome (X-HIGM) is a rare genetic disorder characterized by a defect in immunoglobulin class switching, leading to elevated IgM levels and decreased or absent IgG, IgA, and IgE. This condition is caused by mutations in the *CD40LG* gene, which encodes the CD40 ligand, a protein essential for T- and B- lymphocyte interaction and the initiation of immunoglobulin class switching. The prevalence of X-HIGM varies across populations but is generally estimated at approximately 1 per 1,000,000 live births. A study by the European Society for Immunodeficiencies reported a prevalence of 1 in 500,000 live births in Europe. In populations with a high frequency of consanguineous marriages, prevalence may be higher. Since *CD40LG* is located on the X-chromosome at Xq26, X-HIGM primarily affects males [1-3].

The new discoveries in primary immunodeficiency diagnostics (PID) have highlighted the possible benefits of genetic diagnosis at an early stage to help manage treatment of X-HIGM. Whole exome sequencing may be of particular value in the cases of PID where it is difficult to distinguish the clinical picture of X- HIGM from other PIDs such as CVID or selective IgA deficiency. Further supporting evidence comes from [4] that found that early genetic screening in infants with severe recurrent infections decreases the time to a diagnosis and improves clinical outcomes by allowing early treatment with immunoglobulin replacement and prophylactic antimicrobials.

In addition, more recently described genotype- phenotype correlations show that intronic and splicing variants of the *CD40LG* gene, like those observed in patients, can have a much wider range of clinical outcomes, from classical X-HIGM to milder variants with residual production of immunoglobulin. In [5] patients with *CD40LG* mutations, non-coding mutations were noted to be particularly difficult to identify based on classical immunologic findings. It also highlights the importance of performing wide- ranging genetic and clinical testing on young people who present with infection and abnormal immunoglobulin levels.

X-HIGM presents with recurrent infections, autoimmune diseases, and malignancies. Standard treatment includes immunoglobulin replacement therapy (IgRT) and hematopoietic stem cell transplantation (HSCT). The benefit of immunoglobulin G replacement therapy (IgRT) is increasingly recognized as a long- term treatment option and not merely as a treatment for maintenance in patients with X- HIGM who are ineligible for HSCT. Recently, [6] reviewed the clinical outcome of IgRT with respect to immune homeostasis, infectious disease burden, and quality of life (QoL) in patients with primary antibody deficiencies, particularly the pediatric age group. This underscores the clinical relevance of IgRT, especially in resource-limited regions or when families decline HSCT due to HSCT-associated risks and benefits.

The goal of this study is to report a clinically and genetically confirmed case of X-linked hyper-IgM syndrome due to a previously unreported intronic variant in the *CD40LG* gene. Through detailed presentation of the patient's diagnostic trajectory, immunologic profile, and therapeutic response to immunoglobulin G replacement therapy, we aim to contribute to the expanding literature on rare primary immunodeficiencies and emphasize the value of early molecular diagnosis in guiding effective treatment strategies.

METHODS

Ethical Approval and Patient Consent

This case report was conducted at the University Medical Center (Astana, Kazakhstan). The study was approved by the Local Ethics Committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient’s legal guardians.

Patient samples and whole-exome sequencing

Genomic DNA from a participant enrolled at the University Medical Center (Astana, Kazakhstan) was extracted using the salting- out method. Whole- exome sequencing was performed using xGen Exome Research Panel v2 (Integrated DNA Technologies). Captured libraries were sequenced on an Illumina NovaSeq 6000 platform.

Bioinformatic analysis

Data analysis included read alignment to the GRCh37/hg19 human reference genome, variant calling, and CNV detection. Variants were classified according to ACMG guidelines and interpreted using the Varsome Clinical platform. Sanger sequencing confirmed identified variants [7].

Treatment and Clinical Monitoring

At 2 years and 8 months of age, the patient began weekly subcutaneous immunoglobulin G replacement therapy (IgRT) at a dose of 100 mg/ kg. Trimethoprim- sulfamethoxazole prophylaxis was administered concurrently. Clinical response was monitored through infection frequency and IgG levels.

Case description

Patient K, a male, was born on May 15, 2020, as the fourth child of his mother's sixth pregnancy. His mother's pregnancy history includes the following: first pregnancy—live birth in 2002, healthy girl; second pregnancy—miscarriage at 6–7 weeks of gestation; third—live birth in 2007, healthy girl; fourth — ectopic pregnancy in 2010; fifth — live birth in 2014, healthy girl (Figure 1). The pedigree illustrates the family history, including the proband's mother, father, and siblings. It shows the fourth pregnancy as ectopic, as indicated by the grey square, and highlights the inheritance pattern of the CD40LG mutation. The other pregnancies are represented as live births (green circles) or miscarriage (empty circle).

The sixth pregnancy was uneventful except for maternal anemia. Delivery occurred at 38– 39 weeks of gestation via Cesarean section. At birth, he weighed 4,650 g and measured 56 cm in length. The early neonatal period was unremarkable.

The proband is indicated by the arrow Squares indicate males, circles indicate females Shaded symbols carry the CD40LG variant Unshaded symbols are unaffected individuals Half-shaded symbols are heterozygous carriers of the gene The gray square is an ectopic pregnancy, and the empty circle is a miscarriage The CD40LG mutation is present in the proband and siblings, supporting the hypothesis that it is inherited along the X-linked line

The child was breastfed for 1 year and 3 months. Immunization with the Bacillus Calmette-Guérin vaccine was initiated at the maternity hospital resulting in a 5-mm scar formation. The vaccination was well-tolerated, with no adverse reactions observed, which is critical given the patient's immunodeficiency.

The family history is unremarkable. The patient's older siblings are healthy, except for the eldest sister, who has a food allergy. From 4 months of age, the patient experienced stool irregularities (foamy, undigested). He was consulted by a gastroenterologist, and cow's milk protein allergy and lactase deficiency were diagnosed. The treatment included a dairy- free diet, enzyme supplements, and probiotics. At 6 months, the patient developed severe pneumonia associated with COVID-19, requiring hospitalization for 1.5 months, including 2 days in the intensive care unit, where he received immunoglobulin therapy.

Since the age of one, the patient has experienced recurrent viral respiratory infections, characterized by symptoms of rhinitis, pharyngitis, and a single episode of laryngitis.

He received outpatient symptomatic treatment, including therapy with inhaled glucocorticosteroids and a combined bronchodilator.

The first episode of otitis media occurred at the age of 1 year and was treated with a broad-spectrum antibiotic. At the age of 1 year and 9 months, the patient developed severe, purulent, recurrent otitis media complicated by tympanic membrane perforation, requiring broad-spectrum antibiotic treatment. After that, the patient experienced recurrent otitis media on a monthly basis, necessitating both inpatient and outpatient broad-spectrum antibiotic therapy. At the age of 2 years and 7 months, immunoglobulin was administered alongside antibiotic

treatment. Since the age of 2 years and 8 months, with the initiation of human immunoglobulin therapy, a positive trend has been observed, with a decrease in the frequency of infections and the absence of complications.

RESULTS

Laboratory results

The laboratory examination revealed a decrease in IgA (0.11 g/ L) and IgG (0.05 g/ L). An elevated level of C3 (1.29 g/ L) and a decreased level of C4 (0.190 g/ L) were also noted. A reduction in B lymphocytes (670 cells/ μL) and T cytotoxic lymphocytes (510 cells/ μL) was observed.

A follow-up immunoglobulin test confirmed persistently low IgG (0.18 g/ L) and a significant increase in IgM (4.62 g/L) (normal range: 0.16–1.22 g/L).

Whole-exome sequencing identified a homozygous variant NM_000074.3:c.409+1_409+19del in the *CD40LG* gene (X-linked), classified as likely pathogenic (Table 1).

The following table describes the pathogenic variant in the CD40LG gene identified through whole-exome sequencing analysis. This NM_000074.3:c.409+1_409+19del variant results in a deletion in the intronic splice site of the CD40LG gene and is observed in the hemizygous state in an affected male proband. The identified mutation affecting the CD40LG gene, which is involved in the X-linked hyper-IgM syndrome, was classified as likely pathogenic according to the American College of Medical Genetics (ACMG) guidelines. The table also provides the gene, zygosity status, predicted molecular consequence, and inheritance pattern for each mutation.

Sanger sequencing confirmed the variant and revealed it to be hemizygous in the proband, heterozygous in two siblings, and not detected in one sibling. The proband's parents declined genetic testing.

The intronic splice-site variant NM_000074.3:c.409+1_409+19del identified in the proband by whole-exome sequencing was confirmed via Sanger sequencing (electropherograms shown) in the proband and three of her siblings. The proband was found to be a hemizygous carrier of the CD40LG variant since the gene is X-linked. Two of the proband's siblings were found to be heterozygous carriers, while one sibling was found to be negative. These chromatograms of nucleotide signal readings show what occurs in the presence and absence of a deletion.

Based on clinical, laboratory, and genetic findings, the patient was diagnosed with X-HIGM associated with the *CD40LG* gene (D89.8).

Treatment

Since the age of 2 years and 8 months, the patient has been receiving subcutaneous immunoglobulin G replacement therapy (IgRT) at 100 mg/ kg weekly, with dose adjustments based on his weight and disease exacerbations. The patient also receives trimethoprim-sulfamethoxazole 240 mg/5 mL, 1.5 mL three times daily.

IgRT therapy in the patient leads to positive dynamics, manifested by a reduced frequency of infections and the absence of complications. Additionally, it helps maintain immunoglobulin G levels within the physiological range (7– 12 g/ L). However, an imbalance in immunoglobulins and a decrease in the main populations of T and B lymphocytes persist.

Figures

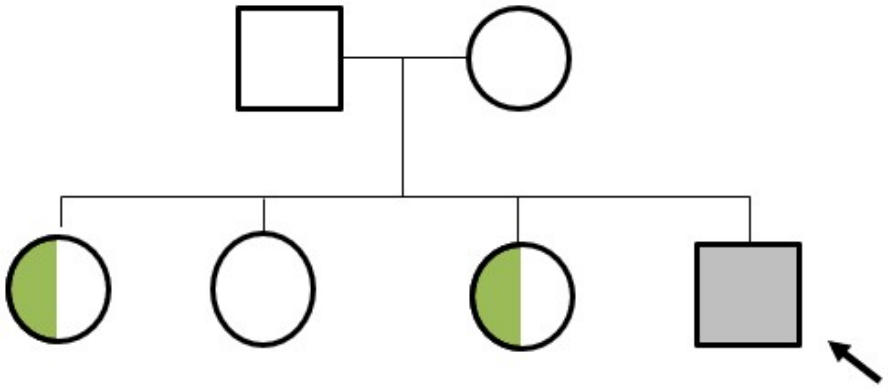


Figure 1: Family pedigree of the proband.

Tables

Variant detected	Gene	Zygosity	Amino acid change	Inheritance	Classification
NM_000074.3:c.409+1_409+19del	*CD40LG*	Hemizygous	Intronic/splicing	X-linked	Likely pathogenic

Table 1: Results of whole-exome sequencing of the patient.

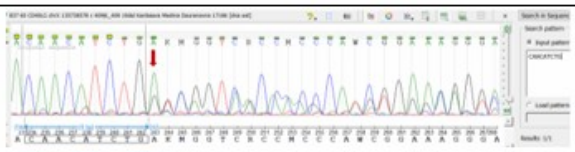
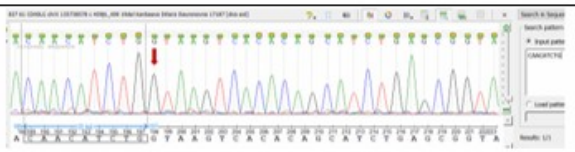
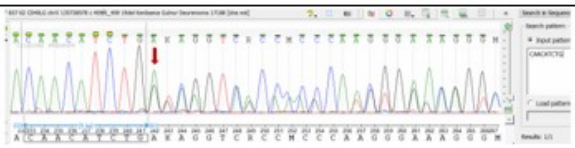
Samples	Sanger sequencing electropherogram	Zygosity of variant NM_000074.3: c.409+1_409+19del
Proband		Hemizygous
Sibling 1		Heterozygous
Sibling 2		Not detected
Sibling 3		Heterozygous

Table 2: Results of Sanger sequencing.

DISCUSSION

The hemizygous c.409+1_409+19del variant identified in the *CD40LG* gene of the proband affects a canonical splice site and is predicted to disrupt normal splicing. This variant has not been previously reported in large population databases (e.g., gnomAD) [8] or submitted to the ClinVar database [9, 10]. Based on its predicted impact and the patient's clinical presentation consistent with X-HIGM, it is classified as likely pathogenic. The variant was confirmed by Sanger sequencing and was identified in a heterozygous state in two of the proband's sisters, confirming carrier status.

CD40LG encodes CD40 ligand, a protein primarily expressed on activated T-cells [11]. CD40 ligand interacts with CD40 on B-cells, playing a crucial role in adaptive immunity by initiating immunoglobulin class switch recombination and somatic hypermutation [12, 13]. The CD40 ligand attaches to its receptor protein, CD40, which is located on the surface of B-cells. The CD40 ligand aids in stimulating B-cells and is necessary for T-cell differentiation [14, 15]. Disruption of *CD40LG* function leads to X-HIGM, a primary immunodeficiency characterized by elevated IgM levels and deficiencies in IgG, IgA, and IgE [16].

X-HIGM is inherited in an X-linked manner, affecting almost exclusively males. Affected males transmit the *CD40LG* variant to all their daughters but none of their sons. Heterozygous females are typically asymptomatic but may exhibit variable manifestations due to X-chromosome inactivation [16]. In simplex cases, the variant may be inherited from a heterozygous mother or arise de novo, occurring in approximately one-third of cases [16].

X- HIGM is clinically characterized by a profound vulnerability to bacterial pathogens and an augmented risk of opportunistic infections, directly attributable to the impaired humoral immune response. Frequent clinical manifestations include respiratory infections such as pneumonia and sinusitis, as well as otitis media. Furthermore, the chronic nature of recurrent infections can contribute to persistent diarrhea and growth retardation [16].

Affected patients may develop neutropenia, autoimmune disorders, gastrointestinal and central nervous system infections, liver disease, neurodegeneration, and an increased risk of neoplasms. Thrombocytopenia and anemia are less commonly observed. Although the total number of circulating B-cells remains normal, there is a significant reduction in class-switched memory B-cells. The severity of X-HIGM varies among affected individuals, even within the same family. Without treatment, this condition can be life-threatening in childhood or adolescence [1,3, 17, 18].

The proband's clinical presentation of recurrent infections, including otitis media and pneumonia, was consistent with the phenotype of X- HIGM. Laboratory investigations revealed hypogammaglobulinemia of IgG and IgA, elevated IgM, and abnormalities in the complement system, further supporting the diagnosis. These findings have important implications for the patient's management, including the initiation of IgRT and consideration of HSCT.

Additionally, the diagnosis enables genetic counseling for the family, allowing for carrier testing and prenatal diagnosis in future pregnancies. While IgRT has shown benefits in managing the proband's infections, HSCT should be considered as a curative option, as it can restore functional CD40 ligand expression and improve immune function in X-HIGM patients.

Notably, IgRT is the mainstay of treatment for X-HIGM. By providing exogenous IgG, IgRT helps restore humoral immunity and reduce the frequency and severity of infections [1]. Our patient responded well to IgRT, experiencing a significant decrease in infections and an overall improvement in health. This case highlights the effectiveness of IgRT in managing X-HIGM and enhancing the quality of life [19].

While IgRT is an effective treatment, HSCT remains the only curative therapy for X-HIGM. HSCT can restore functional CD40 ligand expression and reconstitute the immune system, leading to long-term disease control.

The patient's parents were repeatedly advised on the necessity of hematopoietic stem cell transplantation (HSCT), but after the initiation of baseline therapy, the child's quality of life significantly improved, and no severe infections have occurred. Given the potential risks of complications associated with HSCT, they chose to decline the procedure.

This case report underscores the critical importance of early diagnosis and prompt initiation of human immunoglobulin replacement therapy in patients with X- HIGM. While HSCT offers a potential cure, IgRT serves as an effective alternative, particularly when HSCT is inaccessible or unsuitable. The successful management of patients with IgRT highlights its efficacy in controlling infections and improving quality of life. Additionally, this case further emphasizes the indispensable role of genetic testing in providing a definitive diagnosis, facilitating accurate genetic counseling, and guiding personalized treatment strategies for patients with primary immunodeficiencies. The identification of the c.409+1_409+19del variant in *CD40LG* expands our understanding of the genetic basis of this disorder and highlights the need for continued research in this field.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection

and analysis were performed by Nurgul Sikhayeva, Svetlana Volodchenko and Elena Kovzel. The first draft of the manuscript was written by Gulnar Tortayeva and Elena Sagandykova, all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Generative AI Statement

The author(s) declare that Generative AI tools were used to enhance the language clarity of this work. We take full responsibility for the accuracy and integrity of the content.

ETHICS STATEMENT

The informed consent form and procedures were reviewed and approved by the Local Ethics Committee of the University Medical Center (Astana, Kazakhstan). The study adhered to the ethical principles of the Declaration of Helsinki and the legal standards of Kazakhstan, ensuring academic freedom, intellectual integrity, and the right to publish findings.

Consent to Participate

All participants were fully informed about the objectives, procedures, and potential implications of the study, and voluntary participation was ensured through informed consent. For children, informed consent was obtained from parents.

Data availability Statement

Due to the presence of potentially identifying participant information, all relevant data are available to qualified researchers upon request to the corresponding author Nurgul Sikhayeva (sikhayevanurgul@gmail.com).

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