Aslı Güner Öztürk Demir et al. JBC Genetics. 2024;7(2):114-117.
DOI: 10.24911/JBCGenetics.183-1726230535

CASE REPORT

A novel heterozygous mutation in the SYK gene and systemic inflammation with immunodeficiency - a case report

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ABSTRACT

Background: The spleen tyrosine kinase (SYK) gene, located on chromosome 9q22.2, encodes a crucial cytoplasmic nonreceptor tyrosine kinase involved in immune cell signaling, particularly in B and T cell receptor pathways. Mutations in *SYK* are linked to "Immunodeficiency 82 with Systemic Inflammation" (OMIM: 619381), characterized by systemic inflammation and immune dysfunction.

Case Presentation: We report a case of a 9-year-old boy with a newly identified heterozygous mutation in the *SYK* gene, p.R434Q (c.1301G>A). The patient presented with hypogammaglobulinemia, CD8 deficiency, and immune dysfunction, alongside a history of periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome. Although initial genetic and immunological evaluations were unremarkable, exome sequencing ultimately revealed the novel p.R434Q mutation, which was confirmed through Sanger sequencing.

Conclusion: This case expands the known spectrum of SYK-related disorders and highlights the critical role of genetic testing in the diagnosis and management of immune deficiency syndromes.

Keywords: *SYK*, systemic inflammation, immunodeficiency.

Introduction

The spleen tyrosine kinase (SYK) gene is located at position q22.2 on chromosome 9 and is primarily expressed in hematopoietic-origin cells (1). SYK is a 72-kDa cytoplasmic nonreceptor tyrosine kinase (2,3). SYK, a member of the Src family, is essential for signaling through B cell receptors and Fc receptors and functions in parallel with its homolog, the tyrosine-protein kinase Zap70, in T cell receptor (3). Consequently, SYK mediates various cellular responses, including proliferation, differentiation, and phagocytosis, primarily involved in adaptive immune receptor signaling (4).

Monoallelic mutations in the *SYK* gene are responsible for the "Immunodeficiency 82 with Systemic Inflammation" phenotype (5). "Immunodeficiency 82 with Systemic Inflammation" (OMIM: 619381) is a complex immunological disease characterized by noninfectious inflammation manifesting as gastritis, colitis, lung, liver, or skin disease, and lymphocytic organ infiltration, in addition to recurrent infections with various organisms. One of the most common features is inflammation of the stomach and intestines. In most patients, symptoms are observed in infancy or early childhood. The severity varies. There may be accompanying fever, high white blood cell count, decreased B cells, hypogammaglobulinemia, increased C-reactive protein (OMIM:123260), and a generalized hyperinflammatory state. Variable B and T cell abnormalities, such as abnormal subgroup distribution, are observed on immunological examination. Patients are at increased risk of developing lymphoma in adulthood. Data on treatments with SYK inhibitors have reported regulation of cell abnormalities and clinical improvement in mice (5).

In this case report, we present a novel heterozygous mutation in the *SYK* gene that has not been previously reported. Given the limited information in the literature regarding immunodeficiency and systemic inflammation

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Received: 13 September 2024 | **Accepted:** 12 December 2024

caused by the *SYK* gene, this report is considered a valuable presentation to shed light on the subject.

Case Presentation

A 9-year-old boy from an unrelated family was referred to our genetic diagnosis center due to hypogammaglobulinemia, CD8 deficiency, and immunodeficiency. His family first noticed his condition at 1.5 years of age. Physical examination did not reveal any significant features. The patient did not have a history of frequent infections. He had periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome four times in 2022 and was monitored by the rheumatology department. The genetic panel for periodic fever syndromes (PAD Panel) and severe combined immunodeficiency tests performed on the patient was found to be normal.

Karyotyping and DiGeorge FISH studies were also performed, and no abnormalities were observed in the tests. There is no similar clinical history in his family. The patient has relatives with a history of uterine cancer and lymphoma, and the patient's father has a history of laryngeal cancer. The patient's demographic data, family history, and the comparison of SYK gene clinical findings with the patient's condition are summarized in Table 1.

After the family provided written informed consent for testing and use of clinical and genetic data, a peripheral blood sample was obtained from the patient. DNA was extracted using commercially available kits. Exome sequencing was performed using the Illumina NovaSeq 6000 sequencing machine to detect gene mutations, including all point mutations, minor insertions, and

Table 1. *Summary of patient demographics, family history, and comparison of SYK gene clinical findings with the patient's condition.*

	Our case
Sex	Male
Age at diagnosis	11
Age at onset	1.5
Consanguineous marriage	-
Clinical features	Fever Immunodeficiency Hypogammaglobulinemia Low or normal T cells

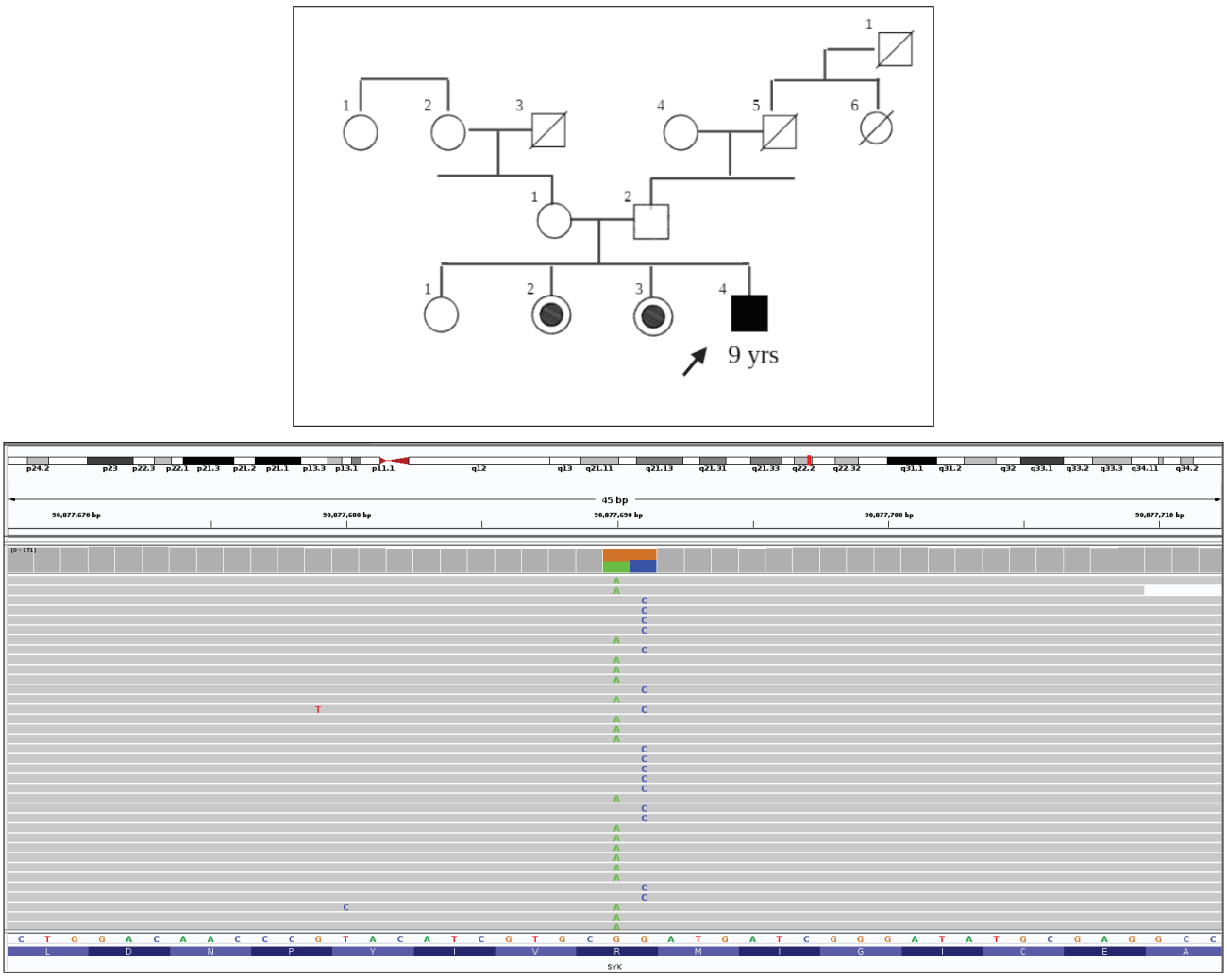

Figure 1. *Pedigree and genetic test results of the patient. DNA sequence of the SYK gene containing the p.R434Q (c.1301G>A) mutation in the patient. The mutation is indicated by the red arrow.*

minor deletions. The results showed that the patient had a mutation in the SYK gene (NM_003177.5); specifically, the base at position 1,301 in the coding region was a guanine-to-adenine (G-to-A) mutation, resulting in a substitution of arginine to glutamine at position 434 (c.1301G>A, p.R434Q) on chromosome 9 (chr9:90877690-90877690).

We found a heterozygous sequence variant in the patient's *SYK* gene at chr9:90877690-90877690 (p.R434Q (c.1301G>A)) that converts G to A (Figure 1).

Discussion

In this case report, the relationship between the p.R434Q mutation in the *SYK* gene and immunodeficiency and systemic inflammation is discussed. It is believed that the p.R434Q mutation in the *SYK* gene leads to hypogammaglobulinemia, CD8+ T cell deficiency, and general signs of immunodeficiency. Mutations in the *SYK* gene have been known to contribute to the development of allergic and autoimmune diseases, as well as hematological malignancies such as B-cell lymphomas (2). These conditions are typically associated with excessive and uncontrolled activation of the immune system, and the role of *SYK* in regulating these mechanisms is increasingly recognized.

Yi et al. (6) investigated the regulation of inflammatory responses by the *SYK* and MyD88 (myeloid differentiation primary-response gene 88) signaling pathways in macrophages. The interaction between these two pathways activates inflammatory transcription factors such as NF-kB, triggering a robust inflammatory response. The study demonstrates that the Syk-MyD88 axis plays a crucial role in the pathogenesis of inflammation-related diseases, including autoimmune diseases, infections, and cancer, and that targeting this pathway could provide potential therapeutic strategies (6). The investigation of the Syk-MyD88 axis supports the notion that the p.R434Q variant in our case may lead to *SYK* overactivation, impairing immune response and resulting in systemic inflammation. These findings are directly related to the changes observed in our case and contribute to understanding the underlying pathological mechanisms.

Wang et al. (7) demonstrated that gain-of-function variants in the *SYK* gene lead to excessive and uncontrolled immune activation, resulting in immune dysregulation and systemic inflammation in both humans and mice. This study supports the idea that the p.R434Q variant could potentially cause *SYK* overactivation, contributing to immunodeficiency and systemic inflammation. Therefore, this study should be considered an important reference supporting the findings in our case.

This case expands the clinical spectrum of *SYK* gene mutations. The *SYK* gene mutation described in this case has not been previously reported in the literature. This genetic change is associated with systemic inflammation and immunodeficiency, highlighting its significance in clinical management. In addition, this case emphasizes the need for further research and genetic testing in the diagnosis and management of diseases associated with *SYK* gene mutations. Collecting more data on new *SYK* gene mutations could help improve the understanding and management of these conditions.

Conclusion

This case presents a novel mutation in the *SYK* gene associated with immunodeficiency and systemic inflammation. Further research on the functions of the *SYK* gene and its mutations could enhance the understanding and development of treatment strategies for such genetic disorders.

List of Abbreviations

DNA	Deoxyribonucleic acid
FISH	Fluorescence in situ hybridization
MyD88	Myeloid differentiation factor 88
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OMIM	Online Mendelian Inheritance in Man
PAD	Periodic fever syndromes
SYK	Spleen tyrosine kinase
Zap70	Zeta-chain associated protein kinase 70

Declaration of conflicting interests

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Funding

The authors declared that this study has received no financial support.

Consent for publication

Informed consent was obtained from the patient's legal guardians.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author's contributions

A.A.: surgical and medical practice. A.G.Ö.D.: concept, data collection and/or processing, and literature search. A.G.Ö.D, A.A, and M.E: design and writing. A.G.Ö.D and A.A: analysis and/or interpretation.

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Reference

1. Blancato J, Smith J, Johnson R, Lee Y. The SYK gene and its role in hematopoietic cells. J Immunol. 2014;192(5):1880–90.
2. Mócsai A, Zhang X, Saijo K. Spleen tyrosine kinase (SYK) in immune cell signaling. Nat Rev Immunol. 2010;10(9):681–92.
3. Zhao J, Liu Z, Yu J. Recent advances in understanding the role of SYK in immune cell signaling. Front Immunol. 2022;13:742684. https://doi.org/10.3389/fimmu.2022.742684

4. Gao Y, Brown T, Wang L, Turner M. Function of spleen tyrosine kinase in adaptive immune responses. Immunol Rev. 2018;281(1):38–54.
5. Sivanand A, Mehta A, Choudhury S. Immunodeficiency 82 with systemic inflammation: a review of SYK-related disorders. Clin Immunol. 2019;208:63–70.
6. Yi YS, Kim HG, Kim JH, Yang WS, Kim E, Jeong D, et al. Syk-MyD88 axis is a critical determinant of inflammatory-response in activated macrophages. Front Immunol. 2021 Dec;12:767366. https://doi.org/10.3389/fimmu.2021.767366
7. Wang X, Zhao Y, Li J, Zhang R. Gain-of-function variants in SYK cause immune dysregulation and systemic inflammation in humans and mice. Nat Commun. 2021;12(1):4567. https://doi.org/10.1038/s41467-021-24851-8