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Letter to the Editor

Bacterial Infections in a Child with TD-β-thalassemia and Common Variable Immunodeficiency Due to a Novel *NFKB1* Variant

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To the editor.

The nuclear factor of the kappa-light polypeptide-gene-enhancer in B cells (NF-κB) signaling pathway is important for regulating immune responses, inflammation, cell survival, and proliferation.[1] The central components in this pathway consist of five transcription factors (REL-B, c-REL, REL-A/p65, NF-κB1, and NF-κB2).[1,2] The *NFKB1* gene encodes the precursor, p105, which is co-translationally processed into the transcriptionally-active p50 subunit.[3] Heterozygous *NFKB1* mutations causing p50 haploinsufficiency have previously been associated with common variable immunodeficiency (CVID).[4] Here, we present CVID in a child with thalassemia major due to an *NFKB1* mutation, the first report of the variant associated with a clinical phenotype.

The proband is a 16-year-old girl with transfusion-dependent β-thalassemia. The family history was unremarkable, and the parents were non-consanguineous. She first developed symptoms of anemia at eight months of age. A composite heterozygotes *HBB* mutation (IVS-II-654/HbE) was detected in the thalassemia gene. She subsequently became transfusion-dependent. At seven years of age, the girl underwent a splenectomy but did not appear to benefit because the blood transfusion requirement did not decrease. In the ensuing years, the child continued to receive regular blood transfusions, requiring an average of 2–4 units of blood every month to maintain a hemoglobin > 9.0 g/dL.

The child did not develop severe infections until 13 years of age when she presented with recurrent respiratory tract infections often accompanied by reactive lymphoid hyperplasia requiring antibiotic treatment. Specifically, the girl had several severe infections, including a perianal abscess, fistula, klebsiella pneumoniae pneumonia, lymph node and liver abscesses, and sepsis. During this time, she had normal B cells based on immunophenotyping; however, intravenous immunoglobulin was occasionally required to treat hypogammaglobulinemia. Additionally, the girl had an increased need for blood transfusions, with an average transfusion of 6–8 units every month.

At 16 years old, she received thalidomide therapy for thalassemia in our hospital. After thalidomide treatment, the transfusion interval increased, but due to another liver abscess after four months, thalidomide treatment was discontinued.

Given the unclear etiology of the immunodeficiency, next-generation sequencing (NGS) was performed on the girl and her parents to detect underlying variants associated with immunodeficiency. The proband was shown to be heterozygous for an *NFKB1*: c.703G>T mutation, which was confirmed by Sanger sequencing (**Figure 1**). The c.703G>T mutation led to a substitution of a conserved valine to leucine at the 235 residue (p.V235L) in the rel homology domain (RHD) of the NFKB1 protein. The father was a wild type at this position. Genetic analysis revealed the same *NFKB1* mutation in the proband's mother; however, she did not show clinical signs of immunodeficiency. Ultimately, we considered CVID associated with the *NFKB1* mutation, and the child was regularly treated with intravenous immunoglobulin (400–600 mg/kg).

CVID is the most common primary immunodeficiency disorder. CVID is a diagnosis of exclusion based on clinical and immunologic criteria. Moreover, CVID is a clinically and genetically heterogeneous disorder characterized by susceptibility to infection, a poor vaccine response, hypogammaglobulinemia, and immune dysregulation.[5] Despite the increasing use of NGS, only a subset of CVID cases have a known underlying genetic cause. In recent years, haploinsufficiency of *NFKB1* has been identified as a novel genetic etiology of a CVID subtype. NFKB1-deficient patients present considerable clinical and immunologic heterogeneity. The clinical spectrum also expands the possible disease manifestations in almost any organ system. NFKB1 haploinsufficiency was first described in three families with CVID who

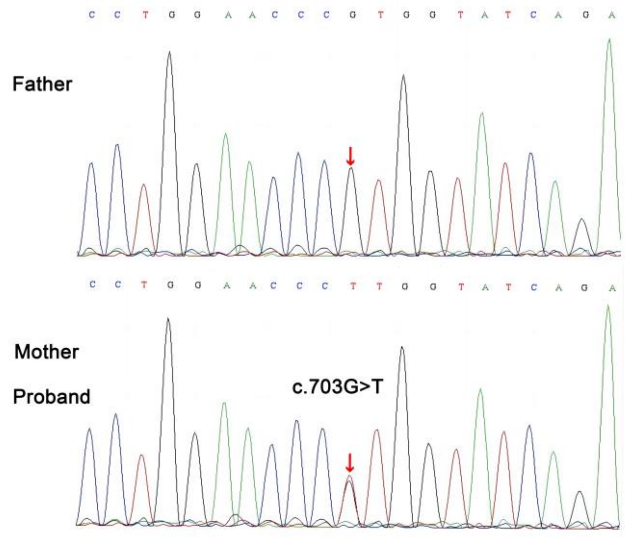

Figure 1. Sanger sequencing chromatogram demonstrating a *NFKB1*: c.703G>T mutation.

presented heterogeneously with symptoms of increased infectious susceptibility, skin lesions, malignant lymphoproliferation, and autoimmunity.[4] The mutations all led to rapid degradation of the mutant protein, resulting in a p50 haplodeficiency state. Since then, >50 other mutations have been reported that are distributed in different regions of NFKB1, most of which are located in the RHD.[6] The c.703G>T mutation is also in the RHD of the NFKB1 protein. Our proband mainly manifested with hypogammaglobulinemia and increased susceptibility to infections. Interestingly, the mother carried the same heterozygous *NFKB1* mutation but was not affected clinically, consistent with significant phenotypic disease heterogeneity. Further work is required to clarify the mechanisms of action of this novel variant. Given the heterogeneity of the disease, treatment cannot be uniform and needs to be adapted to the presentation of individual patients. In addition, the severity and complications of the disease can increase over time and be favored by other concomitant factors, so a closer follow-up is strongly recommended.

Our patient was submitted to splenectomy; given the role of the spleen in immune competence and blood filtration, there is a high risk of post-splenectomy infection.[7,8] Risk of post-splenectomy sepsis depends greatly on the child's primary disease, especially underlying immunodeficiency.[9-11] Thus, splenectomy may increase the immunodepression caused by haploinsufficiency of *NFKB1* mutation in our proband. During thalidomide treatment for thalassemia, the child developed another liver abscess, further suggesting that in addition to the *NFKB1* mutation, immunosuppressive treatment may have impaired the T-cell response and, in combination with the lack of B cells, contributed to the pathogenesis of opportunistic infections. Therefore, physicians considering immunosuppressants for patients with CVID should be vigilant for these risks and take precautions.

We have expanded the genotypic and phenotypic spectra of *NFKB1* mutations. In particular, we provide valuable insights into the possible effect of CVID on the treatment choice for thalassemia.

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References:

1. Beinke S, Ley SC. Functions of NF-kappaB1 and NF-kappaB2 in immune cell biology. Biochem J. 2004;382:393-409. https://doi.org/10.1042/BJ20040544 PMid:15214841 PMCid:PMC1133795
2. Oeckinghaus A, Ghosh S. The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb Perspect Biol. 2009;1:a000034. https://doi.org/10.1101/cshperspect.a000034 PMid:20066092 PMCid:PMC2773619
3. Pereira SG, Oakley F. Nuclear factor-kappaB1: regulation and function. Int J Biochem Cell Biol. 2008;40:1425-30. https://doi.org/10.1016/j.biocel.2007.05.004 PMid:17693123
4. Fliegauf M, Bryant VL, Frede N, Slade C, Woon ST, Lehnert K, Winzer S, Bulashevska A, Scerri T, Leung E, Jordan A, Keller B, de Vries E, Cao H, Yang F, Schaffer AA, Warnatz K, Browett P, Douglass J, Ameratunga RV, van der Meer JW, Grimbacher B. Haploinsufficiency of the NF-kappaB1 Subunit p50 in Common Variable Immunodeficiency. Am J Hum Genet. 2015;97:389-403. https://doi.org/10.1016/j.ajhg.2015.07.008 PMid:26279205 PMCid:PMC4564940
5. Szczawinska-Poplonyk A, Schwartzmann E, Bukowska-Olech E, Biernat M, Gattner S, Korobacz T, Nowicki F, Wiczuk-Wiczewska M. The pediatric common variable immunodeficiency - from genetics to therapy: a review. Eur J Pediatr. 2022;181:1371-83.

https://doi.org/10.1007/s00431-021-04287-6
PMid:34939152 PMCid:PMC8964589
6. Lorenzini T, Fliegauf M, Klammer N, Frede N, Proietti M, Bulashevska A, Camacho-Ordonez N, Varjosalo M, Kinnunen M, de Vries E, van der Meer JWM, Ameratunga R, Roifman CM, Schejter YD, Kobbe R, Hautala T, Atschekzei F, Schmidt RE, Schroder C, Stepensky P, Shadur B, Pedroza LA, van der Flier M, Martinez-Gallo M, Gonzalez-Granado LI, Allende LM, Shcherbina A, Kuzmenko N, Zakharova V, Neves JF, Svec P, Fischer U, Ip W, Bartsch O, Baris S, Klein C, Geha R, Chou J, Alosaimi M, Weintraub L, Boztug K, Hirschmugl T, Dos Santos Vilela MM, Holzinger D, Seidl M, Lougaris V, Plebani A, Alsina L, Piquer-Gibert M, Deya-Martinez A, Slade CA, Aghamohammadi A, Abolhassani H, Hammarstrom L, Kuismin O, Helminen M, Allen HL, Thaventhiran JE, Freeman AF, Cook M, Bakhtiar S, Christiansen M, Cunningham-Rundles C, Patel NC, Rae W, Niehues T, Brauer N, Syrjanen J, Seppanen MRJ, Burns SO, Tuijnenburg P, Kuijpers TW, BioResource N, Warnatz K, Grimbacher B, BioResource N. Characterization of the clinical and immunologic phenotype and management of 157 individuals with 56 distinct heterozygous NFKB1 mutations. J Allergy Clin Immunol. 2020;146:901-11.
https://doi.org/10.1016/j.jaci.2019.11.051
PMid:32278790 PMCid:PMC8246418
7. Leone G, Pizzigallo E. Bacterial Infections Following Splenectomy for Malignant and Nonmalignant Hematologic Diseases. Mediterr J Hematol Infect Dis. 2015;7:e2015057.
https://doi.org/10.4084/mjhid.2015.057
PMid:26543526 PMCid:PMC4621170
8. Iolascon A, Andolfo I, Barcellini W, Corcione F, Garcon L, De Franceschi L, Pignata C, Graziadei G, Pospisilova D, Rees DC, de Montalembert M, Rivella S, Gambale A, Russo R, Ribeiro L, Vives-Corrons J, Martinez PA, Kattamis A, Gulbis B, Cappellini MD, Roberts I, Tamary H, Working Study Group on Red C, Iron of the EHA. Recommendations regarding splenectomy in hereditary hemolytic anemias. Haematologica. 2017;102:1304-13.
https://doi.org/10.3324/haematol.2016.161166
PMid:28550188 PMCid:PMC5541865
9. Rubin LG, Schaffner W. Clinical practice. Care of the asplenic patient. N Engl J Med. 2014;371:349-56.
https://doi.org/10.1056/NEJMcp1314291
PMid:25054718
10. Davies JM, Lewis MP, Wimperis J, Rafi I, Ladhani S, Bolton-Maggs PH, British Committee for Standards in H. Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: prepared on behalf of the British Committee for Standards in Haematology by a working party of the Haemato-Oncology task force. Br J Haematol. 2011;155:308-17.
https://doi.org/10.1111/j.1365-2141.2011.08843.x
PMid:21988145
11. Luoto TT, Pakarinen MP, Koivusalo A. Long-term outcomes after pediatric splenectomy. Surgery. 2016;159:1583-90.
https://doi.org/10.1016/j.surg.2015.12.014
PMid:26832988