

CASE REPORT

Open Access



A novel 268 kb deletion combined with a splicing variant in *IL7R* causes of severe combined immunodeficiency in a Chinese family: a case report

Lulu Yan¹, Yan He², Yuxin Zhang¹, Yingwen Liu¹, Limin Xu², Chunxiao Han¹, Yudan Zhao² and Haibo Li^{1*}

Abstract

Background Severe combined immunodeficiency (SCID) is a group of fatal primary immunodeficiencies characterized by the severe impairment of T-cell differentiation. *IL7R* deficiency is a rare form of SCID that usually presents in the first months of life with severe and opportunistic infections, failure to thrive, and a high risk of mortality unless treated. Although recent improvements in early diagnosis have been achieved through newborn screening, few *IL7R*-related SCID patients had been reported in the Chinese population.

Case presentation Here, we retrospectively analyzed a case of SCID in a 5-month-old girl with symptoms, including severe T-cell depletion, recurrent fever, oral ulcers, pneumonia, hepatosplenomegaly, bone marrow hemophagocytosis, and bacterial and viral infections. Whole-exome sequencing (WES), quantitative PCR (qPCR), and chromosome microarray analysis (CMA) were performed to identify the patient's genetic etiology. We identified a 268 kb deletion and a splicing variant, c.221 + 1G > A, in the proband. These two variants of *IL7R* were inherited from the father and mother.

Conclusions To our knowledge, this is the first report of whole *IL7R* gene deletion in combination with a pathogenic splicing variant in a patient with SCID. This deletion also expands the pathogenic variation spectrum of SCID caused by *IL7R*. The incorporation of exome-based copy number variant analysis makes WES a powerful molecular diagnostic technique for the clinical diagnosis of pediatric patients.

Keywords *IL7R*, Severe combined immunodeficiency, Whole exome sequencing, Chromosome microarray analysis, Splicing variant

*Correspondence:

Haibo Li
doctor_lihb075@sina.com

¹The Central Laboratory of Birth Defects Prevention and Control, Ningbo Women and Children's Hospital, Ningbo, Zhejiang 315000, China

²Department of Pediatrics, Ningbo Women and Children's Hospital, Ningbo, Zhejiang 315000, China



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Severe combined immunodeficiency (SCID) is a life-threatening condition leading to early infant death as a result of severe infection, due to impaired T lymphocyte differentiation [1, 2]. The prevalence of SCID is approximately 1 in 58,000 live births [3]. Early diagnosis before the onset of severe infections is key to the successful management of SCID, and prompt treatment in the first year of life results in the best outcomes [4, 5]. Hematopoietic stem cell transplantation is currently the standard treatment [6]. SCID is genetically heterogeneous, and defects in more than 30 genes have been identified to be causative of SCID, including defects in genes involved in antigen receptor gene rearrangement, T-cell receptor signaling, T-cell differentiation, thymic development, and thymic egress of T-cells [7, 8]. Biallelic variations in the *IL7R* gene abolish T cell development and function, resulting in SCID. *IL7R* deficiency causes T⁻B⁺NK⁺ SCID, which is responsible for 10% of the SCID cases [9–11]. Over 60 patients with SCID with *IL7R* deficiency have been reported worldwide since it was first described by Puel et al. in 1998 [2, 9, 10, 12–23].

The human *IL7R* gene is located at 5p13.2 and consists of two subunits, the IL7R alpha chain (IL7R α) and common gamma chain (γ c). It is expressed on lymphoid cells and plays an important role in the development, survival, homeostasis, and proliferation of T cells [24, 25]. Currently, in addition to the detection of conventional small insertions/deletions (indels) and single nucleotide variants (SNVs), exome-based copy number variant (CNV) analysis makes whole exome sequencing (WES) a powerful tool for the clinical diagnosis of genetic diseases [26, 27]. Herein, we retrospectively identified compound heterozygous variants in *IL7R*, with a maternal splicing variant, c.221+1G>A, and a paternal 268 kb deletion at 5p13.2 in a Chinese patient with SCID.

Case presentation

The proband (II2) was deceased in May 2011, but there were stored dried blood spots. The proband was a girl, the second daughter of non-consanguineous parents. She was a product of a full-term pregnancy via cesarean delivery, and her birth weight was 3.05 kg. She presented at age 3 months with yellow discoloration of the skin and sclera, tan urine, recurrent fever, oral ulcers, and pneumonia. Physical examination revealed that the patient's spleen was 2 cm below the left costal margin in the mid-clavicular line with a soft and sharp margin, and the liver was 2.5 cm below the right costal margin in the mid-clavicular line. Laboratory examinations revealed a white blood cell count of $10.6 \times 10^9/L$, with 88% neutrophils and 6% lymphocytes, a low hemoglobin level (8.6 g/dL), a high platelet count ($815 \times 10^9/L$), an elevated level of ferritin (732.5 ng/mL) and bilirubin (57.1 μ mol/L), presence of Epstein-Barr virus and Rotavirus, and a positive result for direct anti-human globulin test. Additionally, bone marrow examination revealed active hemophagocytosis (Fig. 1A). She was treated with cefodizime, vancomycin, montmorillonite, and other symptomatic treatments; however, her fever did not subside. The patient died of severe bacterial sepsis two months later. Her older sister (II1) had clinical manifestations similar to those of the proband (recurrent febrile episodes, cough, severe anemia, and abdominal neoplasms), and died at seven months of age.

Dried blood spots were obtained from the proband, and blood samples were obtained from the unaffected parents and siblings after obtaining informed consent. Genomic DNA was extracted from dried blood spots and peripheral blood leukocytes for WES using SureSelect Human All Exon V6 kits (Santa Clara, CA, USA) and a HiSeq2500 sequencer (San Diego, CA, USA). The pathogenic variants were assessed using a protocol issued by the American College of Medical Genetics and Genomics (ACMG) [28]. Co-segregation analysis combined with bioinformatics analysis was used to validate the disease-causing variants.

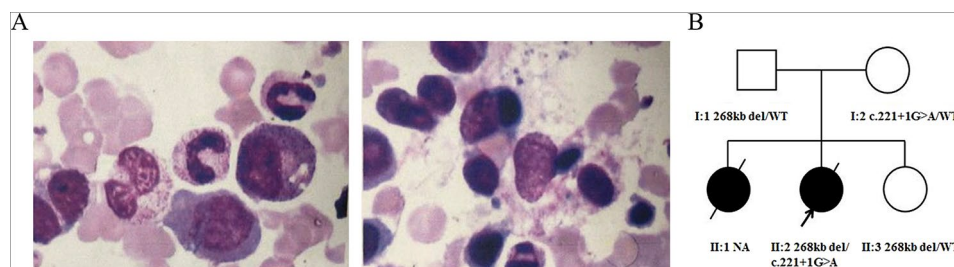


Fig. 1 A Chinese family presents severe combined immunodeficiency (SCID). **A** Bone marrow aspirate smear with features of hemophagocytosis showing neutrophils engulfed by macrophages (Jenner Giemsa, $\times 400$). **B** Pedigree of the family with SCID. Circles and squares indicate females and males respectively; filled symbols represent affected individuals with SCID; slashed symbols are deceased members; open symbols represent healthy individuals. Black arrow indicates the proband. The proband's unaffected mother and father are carriers of the splicing variant and deletion respectively. WT, wild-type; ND, not determined

WES revealed that the proband (II:2) had a novel homozygous variant in *IL7R* (NM_002185.5), c.221+1G>A, which was related to SCID and was previously reported in a Chinese infant [23]. We excluded pathogenic variants of other SCID-associated genes in the European Society for Immunodeficiencies guidelines. According to the ACMG

classification guidelines for sequence variants, the variant c.221+1G>A was classified as pathogenic (PVS1, PM2_Supporting, PM3_Supporting, PP4). Her mother carried the heterozygous splicing variant, while her father (II1) and sister (II3) carried the wild-type alleles (Fig. 1B). This finding was confirmed by Sanger sequencing (Fig. 2A,

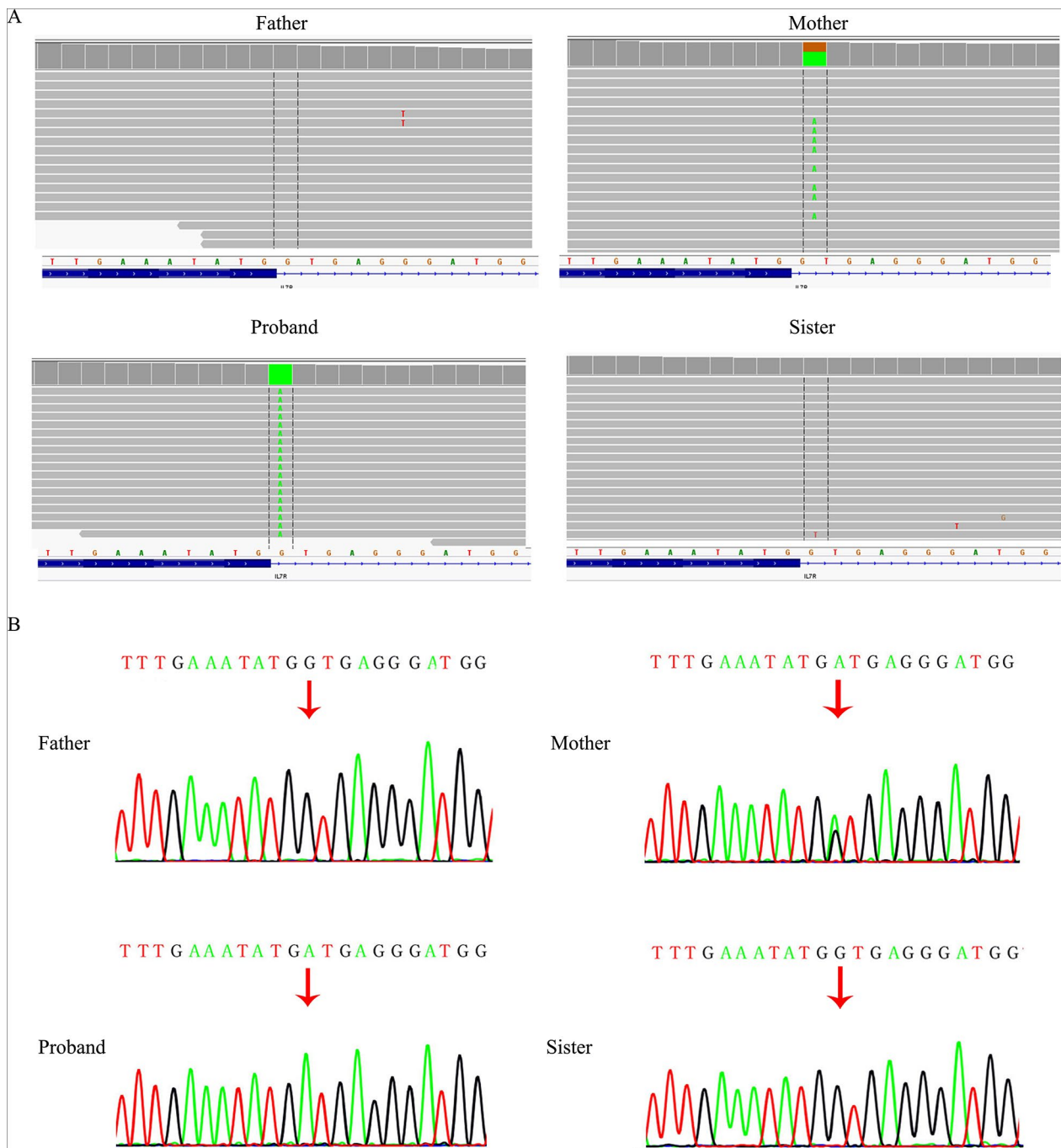


Fig. 2 Identification of a splicing variant in the *IL7R* gene. **A** Whole-exome sequencing (WES) identified the homozygous variant c.221+1G>A in *IL7R* gene (NM_002185.5) in the proband viewed on Integrative Genomics Viewer. Her mother is a carrier of the variant. **B** Sanger sequencing confirmed a homozygous splicing variant c.221+1G>A in the proband. Her mother is a heterozygous variant carrier. Both her father and sister are homozygous for the wild-type allele. The variation site is marked by a red arrow

Table 1 Primers used in qPCR

Region	Location	Name	Sequence (5' → 3')
Exon 1	chr5:35857032–35,857,137	IL7R-qe1F	CATACACACTGGCTCACACA
		IL7R-qe1R	CAGAAACGACTTGAAGTAAAGA
Exon 4	chr5:35871182–35,871,288	IL7R-qe4F	TGAGTGTCTGTATCGGGA
		IL7R-qe4R	GCGGTAAGCTACATCGTGC
Exon8-noncoding region boundaries	chr5:35877593–35,877,687	IL7R-qe9F	CTGCTACCACCCAAGTGC
		IL7R-qe9R	GGTCATGCCTCCTCTCACT

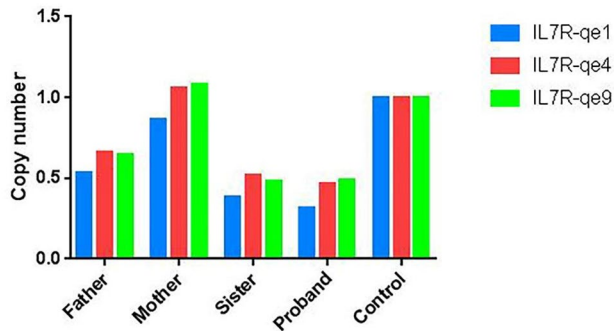


Fig. 3 qPCR (copy number calculated) illustrating the *IL7R* gene deletion in the family. IL7R-qe1, IL7R-qe4, and IL7R-qe9 are three distinct regions of *IL7R* gene. Bar graph shows the calculated copy numbers of DNA from the proband, her father, mother, sister, and normal control by qPCR. The copy number decreased by half in the proband, her father, and sister as compared to the normal control, suggesting a heterozygous deletion of *IL7R* gene

B). The homozygosity of the c.221+1G>A variant in the proband could not be explained unless the other allele was lost. Thus, we analyzed potential CNVs of the *IL7R* gene using WES. Notably, the results suggested that the proband, her father, and sister may have a heterozygous deletion of the *IL7R* gene (NM_002185.5: chr5:35700839-35968226del). To further confirm the deletion of the *IL7R* gene, we performed qPCR. qPCR was performed to amplify *IL7R* exon 1, exon 4 and 8-noncoding region boundaries with three primers sets (Table 1). The *TERT* gene was chosen as the endogenous control in this study. All reactions using SYBR Green Dye were run using the following cycle: 30s at 98 °C, followed by 30 cycles of 10s at 98 °C, 20 s at 56 °C, 30s at 68 °C, and a final incubation at 68 °C for 7 min. All reactions were performed using the ABI 7500 real-time PCR system (Applied Biosystems, USA). All the experiments were replicated three times to ensure the accuracy of the experiment. After qPCR was performed, the copy number data were collected and analyzed using the $2^{-\Delta\Delta CT}$ method. The qPCR results showed that the patient, her father, and her sister had approximately half of copy numbers for exons 1, 4, and 8-noncoding region boundaries of *IL7R* compared to those in the control, suggesting that one of the *IL7R* alleles was entirely deleted. To examine the *IL7R* heterozygous deletion, we performed chromosome microarray

analysis (CMA) on the father and sister (the proband did not have enough DNA samples for CMA) (Fig. 3). The CMA results revealed a 268 kb heterozygous deletion (chr5:35,701,848–35,969,375) on 5p13.2 in samples of the father and sister (Fig. 4). None of the samples exhibited other pathological CNVs, areas of loss of heterozygosity or maternal uniparental disomy. Deletions can be classified as uncertain significance by the ACMG and the Clinical Genome Resource (ClinGen) [29]. The heterozygous deletion in the sister was inherited from her father, suggesting that the proband could have inherited the same 268 kb deletion from her father. Therefore, a homozygous splicing mutation is a heterozygous maternal mutation that is unmasked by a heterozygous paternal deletion.

Discussion and conclusion

Currently, the combination of pathogenic variant screening and CNV calling has been increasingly used in WES, which largely improves the detection efficiency for the diagnosis of inherited diseases [30, 31]. Recent technological advances have enabled CNV calling from WES data using accurate and highly sensitive bioinformatics tools [32, 33]. Here, we identified a novel 268 kb deletion in the *IL7R* gene combined with a splicing variant, (c.221+1G>A), as the cause of the SCID phenotype in a female patient. The deletion was paternally inherited and the c.221+1G>A variant was maternally inherited.

The likely pathogenic and pathogenic variants of *IL7R* associated with SCID in the ClinVar database included 14 missense, 10 nonsense, seven frameshift, six splicing variants, and one synonymous variant (Fig. 5). The c.221+1G>A splicing variant detected in our patient also has been included in the ClinVar database. *IL7R* contains three major domains: a transmembrane, an intracellular, and an extracellular domain. The extracellular domain is important for binding to IL-7 and belongs to one of the variable loop regions in the protein structure that is assumed to control the binding specificity of *IL7R* [34, 35]. Mutated *IL7R* may impair IL-7 signal transduction in T cell and cause T-cell deficiency.

The *IL7R* gene contains eight exons. Previously identified single- or multi-exon deletions in *IL7R* are common in T-B+NK+SCID and detectable by WES analysis. We identified 8 cases of the exon deletions of *IL7R* detected

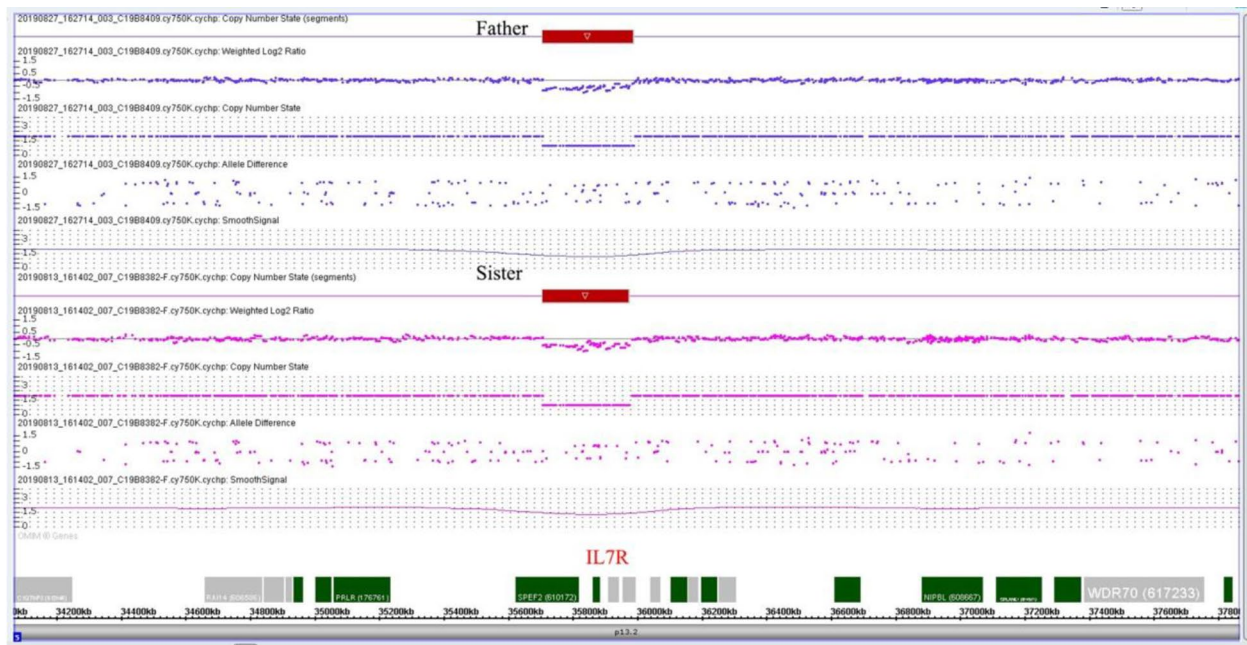


Fig. 4 Chromosome microarray analysis results of the sister and father revealed a 286 kb heterozygous deletion (chr5:35,701,848 – 35,969,375) involving the *IL7R* gene located at 5p13.2. The deletion is identified by a downshift of the probes in the deleted region

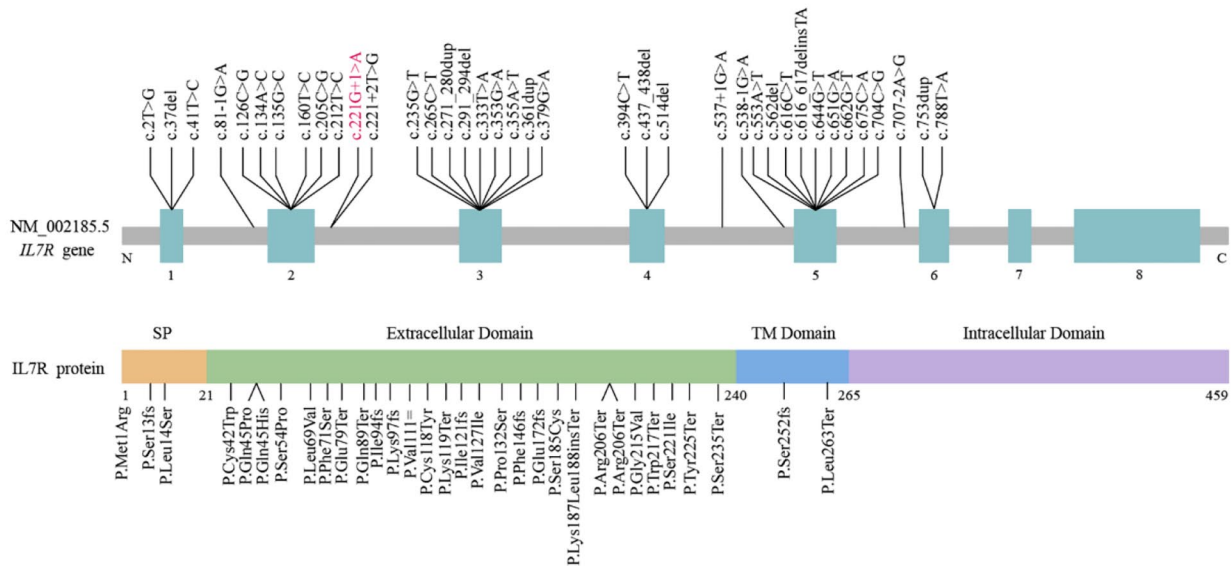


Fig. 5 Distribution of *IL7R* domains and all likely pathogenic and pathogenic variants associated with SCID in ClinVar database. The reported variants are indicated in red (<https://www.ncbi.nlm.nih.gov/clinvar/>, the last access time was October 4, 2023)

SCID through a literature review, approximately 100% of T-B+NK+ patients with SCID had compound heterozygous *IL7R* deletions (Exon3del, Exon2-4del), and exon 3 is a deletion hotspot in *IL7R* [17, 21]. Notably, in our study, we reported a heterozygous 268 kb deletion that contained the entire *IL7R* gene in a patient with SCID, emphasizing the importance of identifying CNVs of *IL7R* in such cases. Furthermore, the 268 kb deletion in the

patient also involved three genes adjacent to *IL7R*, *SPEF2*, *CAPSL* and *UGT3A1*, the heterozygous deletion of which did not cause a dominant genetic disorder.

Patients with SCID and impaired *IL7R* function may have immune dysregulation, severe infections, chronic inflammatory diseases, as well as cancer [36]. The main clinical manifestations in the older sister in this study were severe anemia and abdominal neoplasms. However,

the proband presented with the typical clinical symptoms of SCID, including recurrent infections, fever, pneumonia, oral ulcers, and bacterial and viral infections. Additionally, the proband presented with atypical symptoms, including hyperferritinemia, hepatosplenomegaly, and bone marrow hemophagocytosis, which overlapped with the symptoms of hemophagocytic lymphohistiocytosis (HLH). HLH-like symptoms have not been previously described in SCID cases involving the *IL7R*. The atypical symptoms presented by our patient highlight the diagnostic challenges in the field of SCID. Typically, patients with complete loss of IL-7R present early onset SCID with profound T-cell lymphopenia and normal B and NK cell levels [10]. Unfortunately, we were unable to assess the lymphocyte levels of the patient without an immunological test because she died of bacterial sepsis. To the best of our knowledge, this is the first report of deletion of the entire *IL7R* allele in a Chinese family with SCID. We confirmed that the pathogenic variant c.221+1G>A in one *IL7R* allele is revealed by a 268 kb 5p13.2 deletion of the other allele. The simultaneous detection of SNVs/indels and CNVs in *IL7R* demonstrates the advantage of WES for identifying pathogenic variants and the importance of parental verification.

In conclusion, our patient received a definitive genetic diagnosis of SCID after her death, which was due to a compound heterozygous for the *IL7R* gene with a novel 268 kb deletion and a splice variant. This deletion also expands the pathogenic variation spectrum of SCID caused by *IL7R*. Further functional validation is necessary to clarify the pathogenesis of the *IL7R* gene in SCID.

Abbreviations

SCID	Severe combined immunodeficiency
WES	Whole exome sequencing
qPCR	Quantitative PCR
CMA	Chromosome microarray analysis
CNVs	Copy number variants
Indels	Insertions/deletions
SNVs	Single nucleotide variants
ACMG	American College of Medical Genetics and Genomics
HLH	Hemophagocytic lymphohistiocytosis

Acknowledgements

The authors thank the family for their participation in this research.

Author contributions

LY designed the study and revised the manuscript; YH collected the clinical data; YZ, YL and CH analyzed the WES and CMA data; LX and YZ interpreted the data; and HL provided funding and revised the manuscript. All the authors have read and approved the final version of the manuscript.

Funding

This work was supported by the Medical and Health Project of Zhejiang Province (Grant No. 2020KY890), the Science and Technology Development Program of Ningbo (Grant Nos. 202002N3150 and 2022S035), the Innovation Project of Distinguished Medical Team in Ningbo (Grant No. 2022020405), and the Ningbo Key Technology Research and Development Project (2023Z178).

Data availability

The detected variants have been submitted to the Leiden Open Variation Database (LOVD), at the following link: <https://databases.lovd.nl/shared/individuals/00437939>.

Declarations

Ethics approval and consent to participate

The study was approved by the Ningbo Women and Children's Hospital Hospital Medical Ethics Committee (approval number EC2020-048). Written informed consent to participate was obtained from the parents.

Consent for publication

Written informed consent for the publication of identifying images and other personal or clinical details was obtained from parents.

Competing interests

The authors declare no competing interests.

Received: 19 October 2023 / Accepted: 5 December 2023

Published online: 11 December 2023

References

- de Pagter AP, Bredius RG, Kuijpers TW, Tramper J, van der Burg M, van Montfrans J, Driessen GJ. Overview of 15-year Severe Combined Immunodeficiency in the Netherlands: towards newborn blood spot screening. *Eur J Pediatr*. 2015;174(9):1183–8.
- Liao CY, Yu HW, Cheng CN, Chen JS, Lin CW, Chen PC, Shieh CC. A novel pathogenic mutation on Interleukin-7 receptor leading to Severe Combined Immunodeficiency identified with newborn screening and whole exome sequencing. *J Microbiol Immunol Infect*. 2020;53(1):99–105.
- Al-Herz W, Bousfiha A, Casanova JL, Chapel H, Conley ME, Cunningham-Rundles C, Etzioni A, Fischer A, Franco JL, Geha RS, et al. Primary immunodeficiency Diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Immunol*. 2011;2:54.
- Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, Kapoor N, Hanson IC, Filipovich AH, Jyonouchi S, et al. Transplantation outcomes for Severe Combined Immunodeficiency, 2000–2009. *N Engl J Med*. 2014;371(5):434–46.
- Railey MD, Likhnygina Y, Buckley RH. Long-term clinical outcome of patients with Severe Combined Immunodeficiency who received related donor bone marrow transplants without pretransplant chemotherapy or post-transplant GVHD prophylaxis. *J Pediatr*. 2009;155(6):834–40.
- Pai SY. Treatment of primary immunodeficiency with allogeneic transplant and gene therapy. *Hematol Am Soc Hematol Educ Program*. 2019;2019(1):457–65.
- Picard C, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, Etzioni A, Holland SM, Klein C, et al. Primary Immunodeficiency Diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for primary immunodeficiency 2015. *J Clin Immunol*. 2015;35(8):696–726.
- Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, Etzioni A, Franco JL, Gaspar HB, Holland SM, et al. Primary immunodeficiency Diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Immunol*. 2014;5:162.
- Giliani S, Mori L, de Saint BG, Le Deist F, Rodriguez-Perez C, Forino C, Mazzolari E, Dupuis S, Elhasid R, Kessel A, et al. Interleukin-7 receptor alpha (IL-7Ralpha) deficiency: cellular and molecular bases. Analysis of clinical, immunological, and molecular features in 16 novel patients. *Immunol Rev*. 2005;203:110–26.
- Puel A, Ziegler SF, Buckley RH, Leonard WJ. Defective IL7R expression in T(-) B(+)/NK(+) Severe Combined Immunodeficiency. *Nat Genet*. 1998;20(4):394–7.
- Mazzucchelli RL, Riva A, Durum SK. The human IL-7 receptor gene: deletions, polymorphisms and mutations. *Semin Immunol*. 2012;24(3):225–30.
- Lev A, Simon AJ, Barel O, Eyal E, Glick-Saar E, Nayshool O, Birk O, Stauber T, Hochberg A, Broides A, et al. Reduced function and diversity of T cell

- repertoire and distinct clinical course in patients with IL7RA mutation. *Front Immunol.* 2019;10:1672.
13. Mansour R, Bsati YE, Fadel A, El-Orfali Y, Noun D, Tarek N, Kabbara N, Abboud M, Massaad MJ. Diagnosis and treatment of a patient with Severe Combined Immunodeficiency due to a Novel homozygous mutation in the IL-7Ralpha chain. *Front Immunol.* 2022;13:867837.
 14. Puel A, Leonard WJ. Mutations in the gene for the IL-7 receptor result in T(-) B(+)NK(+) Severe Combined Immunodeficiency Disease. *Curr Opin Immunol.* 2000;12(4):468–73.
 15. Gallego-Bustos F, Gotea V, Ramos-Amador JT, Rodriguez-Pena R, Gil-Herrera J, Sastre A, Delmiro A, Rai G, Elnitski L, Gonzalez-Granado LI, et al. A case of IL-7R Deficiency caused by a Novel Synonymous Mutation and implications for Mutation Screening in SCID diagnosis. *Front Immunol.* 2016;7:443.
 16. Luk A, Lee PP, Mao H, Chan KW, Chen XY, Chen TX, He JX, Kechout N, Suri D, Tao YB, et al. Family history of early infant death correlates with earlier age at diagnosis but not shorter time to diagnosis for Severe Combined Immunodeficiency. *Front Immunol.* 2017;8:808.
 17. Engelhardt KR, Xu Y, Grainger A, Germani BM, Swan DJ, Willet JD, Abd HI, Agyeman P, Barge D, Bibi S, et al. Identification of heterozygous single- and multi-exon deletions in IL7R by whole exome sequencing. *J Clin Immunol.* 2017;37(1):42–50.
 18. Abd HI, Slatter MA, McKendrick F, Pearce MS, Gennery AR. Long-term Health Outcome and Quality of Life Post-HSCT for IL7Ralpha-, Artemis-, RAG1- and RAG2-Deficient Severe Combined Immunodeficiency: a single Center Report. *J Clin Immunol.* 2018;38(6):727–32.
 19. Firtina S, Yin NY, Hatirnaz NO, Kiykim A, Aydiner E, Nepesov S, Camcioglu Y, Sayar EH, Reisli I, Torun SH, et al. Mutational landscape of Severe Combined Immunodeficiency patients from Turkey. *Int J Immunogenet.* 2020;47(6):529–38.
 20. Yu H, Zhang VW, Stray-Pedersen A, Hanson IC, Forbes LR, de la Morena MT, Chinn IK, Gorman E, Mendelsohn NJ, Pozos T, et al. Rapid molecular diagnostics of severe primary immunodeficiency determined by using targeted next-generation sequencing. *J Allergy Clin Immunol.* 2016;138(4):1142–51.
 21. Bayer DK, Martinez CA, Sorte HS, Forbes LR, Demmler-Harrison GJ, Hanson IC, Pearson NM, Noroski LM, Zaki SR, Bellini WJ, et al. Vaccine-associated varicella and rubella infections in Severe Combined Immunodeficiency with isolated CD4 lymphocytopenia and mutations in IL7R detected by tandem whole exome sequencing and chromosomal microarray. *Clin Exp Immunol.* 2014;178(3):459–69.
 22. Roifman CM, Zhang J, Chitayat D, Sharfe N. A partial deficiency of interleukin-7R alpha is sufficient to abrogate T-cell development and cause Severe Combined Immunodeficiency. *Blood.* 2000;96(8):2803–7.
 23. Wang H, Qian Y, Lu Y, Qin Q, Lu G, Cheng G, Zhang P, Yang L, Wu B, Zhou W. Clinical utility of 24-h rapid trio-exome sequencing for critically ill infants. *Npj Genom Med.* 2020;5:20.
 24. Crompton T, Outram SV, Buckland J, Owen MJ. A transgenic T cell receptor restores thymocyte differentiation in interleukin-7 receptor alpha chain-deficient mice. *Eur J Immunol.* 1997;27(1):100–4.
 25. Corcoran AE, Smart FM, Cowling RJ, Crompton T, Owen MJ, Venkitaraman AR. The interleukin-7 receptor alpha chain transmits distinct signals for proliferation and differentiation during B lymphopoiesis. *Embo J.* 1996;15(8):1924–32.
 26. Zhai Y, Zhang Z, Shi P, Martin DM, Kong X. Incorporation of exome-based CNV analysis makes trio-WES a more powerful tool for clinical diagnosis in neurodevelopmental disorders: a retrospective study. *Hum Mutat.* 2021;42(8):990–1004.
 27. Xiang J, Ding Y, Yang F, Gao A, Zhang W, Tang H, Mao J, He Q, Zhang Q, Wang T. Genetic analysis of Children with Unexplained Developmental Delay and/or intellectual disability by whole-exome sequencing. *Front Genet.* 2021;12:738561.
 28. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405–24.
 29. Riggs ER, Andersen EF, Cherry AM, Kantarci S, Kearney H, Patel A, Raca G, Ritter DI, South ST, Thorland EC, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genet Med.* 2020;22(2):245–57.
 30. Tilemis FN, Marinakis NM, Veltra D, Svingou M, Kekou K, Mitrakos A, Tzetzis M, Kosma K, Makrythanasis P, Traeger-Synodinos J, et al. Germline CNV detection through whole-exome sequencing (WES) Data Analysis enhances Resolution of Rare Genetic Diseases. *Genes (Basel).* 2023;14(7).
 31. Testard Q, Vanhoye X, Yauy K, Naud ME, Vieville G, Rousseau F, Dauriat B, Marquet V, Bourthoumieus S, Genevieve D, et al. Exome sequencing as a first-tier test for copy number variant detection: retrospective evaluation and prospective screening in 2418 cases. *J Med Genet.* 2022;59(12):1234–40.
 32. Babadi M, Fu JM, Lee SK, Smirnov AN, Gauthier LD, Walker M, Benjamin DI, Zhao X, Karczewski KJ, Wong I, et al. GATK-gCNV enables the discovery of rare copy number variants from exome sequencing data. *Nat Genet.* 2023;55(9):1589–97.
 33. Tisserant E, Vitobello A, Callegarin D, Verdez S, Bruel AL, Aho GL, Sorlin A, Viora-Dupont E, Konyukh M, Marle N, et al. Copy number variants calling from WES data through eXome hidden Markov model (XHMM) identifies additional 2.5% pathogenic genomic imbalances smaller than 30 kb undetected by array-CGH. *Ann Hum Genet.* 2022;86(4):171–80.
 34. McElroy CA, Holland PJ, Zhao P, Lim JM, Wells L, Eisenstein E, Walsh ST. Structural reorganization of the interleukin-7 signaling complex. *Proc Natl Acad Sci U S A.* 2012;109(7):2503–8.
 35. Vonarbourg C, Diefenbach A. Multifaceted roles of interleukin-7 signaling for the development and function of innate lymphoid cells. *Semin Immunol.* 2012;24(3):165–74.
 36. Cirillo E, Giardino G, Gallo V, D'Assante R, Grasso F, Romano R, Di Lillo C, Galasso G, Pignata C. Severe Combined Immunodeficiency—an update. *Ann NY Acad Sci.* 2015;1356:90–106.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.