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Case report: a case of *CYBB* gene variant in X-linked chronic granulomatous disease

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Abstract

Chronic granulomatous disease (CGD) is an inherited immunodeficiency characterized by impaired phagocytic function due to defects in the NADPH oxidase complex. This enzymatic deficiency compromises the production of reactive oxygen species required for microbial killing, predisposing affected individuals to recurrent and often severe infections. Pulmonary involvement is particularly frequent. We describe a 10-year-old Chinese boy who initially presented with persistent fever and failed to respond adequately to standard therapy, ultimately developing rapidly progressive multi-organ failure. Genetic testing identified a hemizygous variant (c.252G > A) in exon 3 of the X-linked *CYBB* gene, which produces a splicing mutation(p.Ala84=). His mother was confirmed to be a heterozygous carrier. This case underscores the value of molecular diagnostics in confirming X-linked CGD (X-CGD) and highlights the importance of prenatal testing to prevent recurrence in high-risk families.

Keywords Chronic granulomatous disease, *CYBB* gene, NADPH oxidase, Hemophagocytic syndrome, Genetic diagnosis

Background

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency resulting from functional impairment of phagocytes caused by mutations in components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. This defect reduces or abolishes reactive oxygen species generation, a critical mechanism for intracellular killing of microbes [1, 2]. Clinically, CGD is marked by recurrent bacterial and fungal infections, granulomatous inflammation, and increased risk of early mortality. Approximately 65% of cases are X-linked and stem from variants in *CYBB*, which encodes the gp91^{phox} subunit, whereas the remaining cases follow patterns of autosomal recessive inheritance [3, 4]. Early molecular diagnosis and family counseling can improve outcomes by facilitating prompt treatment and informed reproductive decisions. We report a fatal pediatric case of X-CGD and discuss the diagnostic and genetic findings.

Case presentation

A 10-year-old boy was admitted on October 7,2024 with a 12-day history of intermittent fever reaching 40.3 °C, accompanied by bilateral knee pain and right subcostal discomfort. He denied cough, sputum production, headache, or dizziness. Initial assessments at local facilities revealed elevated C-reactive protein (26.1–62.3 mg/L). Chest CT demonstrated a subpleural patchy opacity in the right lower lobe suggestive of inflammation, scattered micronodules in both lungs, and multiple calcified lymph nodes in the mediastinum and left axilla. Empirical therapy with azithromycin, ceftriaxone, and corticosteroids yielded only transient improvement. The patient was the second child of his family (G2P2), conceived via in

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vitro fertilization, delivered at term via vaginal birth, and had normal growth and developmental milestones with timely immunizations. Notably, his older brother died at six years of age from an infection of unspecified etiology.

On admission, he appeared alert but fatigued. Vital signs included a heart rate of 98 beats/min, temperature of 39.2 °C, respiratory rate of 22 breaths/min, blood pressure of 110/68 mmHg. Growth and nutrition were within normal limits. Cardiac and abdominal examinations were unremarkable, and neurologic reflexes were intact. Pulmonary percussion was clear bilaterally, but coarse breath sounds were heard on auscultation. No skeletal abnormalities or lower-limb edema were detected.

Initial laboratory tests showed elevated liver enzymes: alanine aminotransferase 69 U/L (reference 7–30 U/L) and aspartate aminotransferase 68 U/L (14–44 U/L). ESR was increased at 25.0 mm/h (< 15 mm/h). Complete blood count with inflammatory markers showed: leukocytes 9.41×10^9/L ($4.3–11.3 \times 10^9$/L), hemoglobin 136 g/L (118–156 g/L), platelets 250×10^9/L ($167–453 \times 10^9$/L), and C-reactive protein 48.97 mg/L (< 10 mg/L). Chest CT on October 7,2024 revealed signs consistent with bronchitis, multiple bilateral pulmonary nodules, and a patchy opacity in the lower lobe of the right lung suggestive of inflammation (Fig. 1A).

On admission, patient received comprehensive symptomatic management consisting of piperacillin-tazobactam, low-dose methylprednisolone, yanhuning, peramivir, liver hydrolyzed peptide, and correction of electrolyte abnormalities.An electronic bronchoscopy performed on October 9 revealed diffuse tracheobronchial mucosal inflammation, and bronchoalveolar lavage fluid was submitted for next-generation sequencing (NGS). NGS of the lavage fluid identified Pseudomonas aeruginosa and Mycoplasma pneumoniae.Despite these measures, the child experienced intermittent fever, increasing fatigue, and clinical deterioration characterized by dyspnea and orthopnea. Repeat chest CT on October 12, 2024 revealed [1] progression of bronchitic changes with multiple bilateral pulmonary nodules and a mass-like opacity in the right lower lobe compared with the initial scan, and [2] persistent calcification of left axillary lymph nodes (Fig. 1B). Abdominal ultrasound indicates splenomegaly.A rapid cardiac enzyme panel demonstrated an elevated B-type natriuretic peptide precursor (1,122 pg/mL). Comprehensive biochemical testing showed marked liver injury (alanine aminotransferase 431 U/L, aspartate aminotransferase 698 U/L), urea 9.32 mmol/L, creatinine 110.4 μmol/L, leukocytes 0.96 × 10^9/L, hemoglobin 113 g/L, platelets 71 × 10^9/L, PT 23.7 s, APTT 46.0 s, D-dimer 21.21 μg/mL, fibrin degradation products (FDP) 45.07 μg/mL, Fibrinogen 0.5 g/L, ferritin > 2,000 ng/mL, and lactate 8.2 mmol/L (reference 0.5–2.2 mmol/L). Echocardiography revealed left ventricular dilation with mild mitral and tricuspid regurgitation, depressed left ventricular systolic function, and elevated pulmonary artery pressure (38 mmHg). The results indicated hemophagocytosis(According to the HLH-2004 diagnostic criteria[3].The child was urgently transferred to the PICU for further treatment where his condition progressed to multiple organ failure and disseminated intravascular coagulation.Aggressive resuscitation was undertaken, but was unsuccessful.

Despite extensive treatment and rescue efforts, the patient died after four days of hospitalization due to rapidly progressive organ failure. The family raised concerns regarding the diagnostic and therapeutic course. With family consent and approval by the Ethics Committee of the Second Hospital of Lanzhou University, a postmortem examination and genetic testing were performed. Autopsy findings were consistent with hemophagocytic syndrome, showing diffuse nodular necrosis and macrophage infiltration with active inflammation in the lungs; splenomegaly with widespread macrophage proliferation; hepatic enlargement with multifocal stem cell necrosis; cerebral edema; and systemic congestion of multiple organs. Trio-based whole-exome sequencing (Trio-WES) confirmed the presence of a variant in the *CYBB* gene associated with X-linked chronic granulomatous disease (Fig. 2). The variant was maternally inherited.

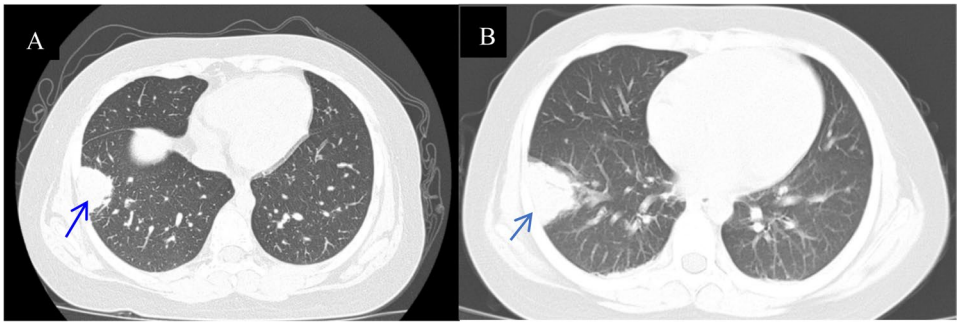

Fig. 1 **A** Chest CT on admission revealed signs consistent with bronchitis, multiple bilateral pulmonary nodules, and a patchy opacity in the lower lobe of the right lung suggestive of inflammation. **B** Chest CT after four days revealed progression of bronchitic changes with multiple bilateral pulmonary nodules and a mass-like opacity in the right lower lobe compared with the initial scan

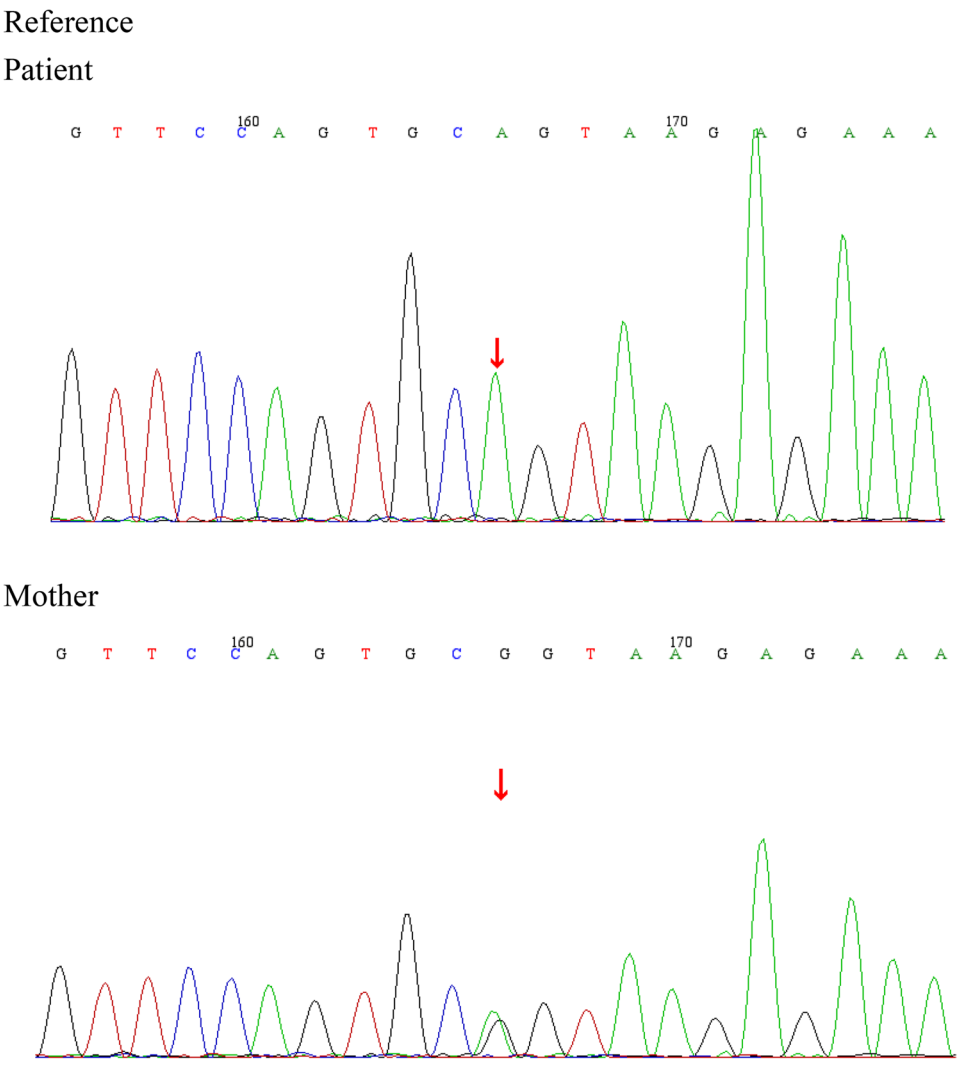

Fig. 2 The patient exhibited a hemizygous variant (c.252G> A) in exon 3 of the CYBB gene on the X chromosome. The patient's mother harbored a heterozygous variant in exon 3 of the CYBB gene on the X chromosome

WES identified a hemizygous pathogenic variant in *CYBB* (chrX:3764 – 2853); specifically a splicing mutation in exon 3 (NM_000397.4: c.252G > A, p.Ala84=). Sanger sequencing confirmed that the variant was inherited from the proband's mother. Following the guidelines of the American College of Medical Genetics and Genomics (ACMG), the variant was classified as " pathogenic" ,and the ClinVar database describes its pathogenicity as pathogenic, granulomatous disease, chronic, X-linked, X-linked Mendelian susceptibility to mycobacterial diseases due to *CYBB* deficiency.

Discussion

CGD is an uncommon hereditary disorder characterized by impaired phagocytic function. Initially described by Charles Janeway in 1954, its underlying defect in the oxidative burst of phagocytes was elucidated in 1967. CGD arises from mutations in genes encoding components of the NADPH oxidase complex, leading to defective production of superoxide radicals [5] and thereby predisposing affected individuals to persistent infections and inflammatory complications [6]. The NADPH oxidase complex comprises five principal subunits designated gp91^{phox}, p22^{phox}, p47^{phox}, p67^{phox}, and p40^{phox}, which are respectively encoded by *CYBB*, *CYBA*, *NCF1*, *NCF2*, and *NCF4* [7–9]. Variants in *CYBB* are inherited in an X-linked manner, whereas defects in the other four genes follow autosomal recessive inheritance [10]. More recently, Chiriaco et al. identified an additional autosomal recessive form linked to *CYBC1/EROS* mutations [6]. The prevalence of CGD in the United States is estimated at approximately 1 in 200,000 live births [11, 12], while the incidence in China remains unclear. Most diagnoses are made in early childhood, typically between 1 and 3 years of age, although the age of onset may vary.

X-CGD primarily affects males and frequently manifests in infancy, though later onset into adolescence or adulthood has been reported in European and North American cohorts. This discrepancy may reflect differences in vaccination practices and early-life exposures. Notably, in China, all newborns routinely receive Bacillus Calmette-Guérin (BCG) immunization [13, 14]. Female carriers are generally asymptomatic, but rare cases of symptomatic heterozygotes have been documented due to skewed X-chromosome inactivation. Recurrent infections, including febrile episodes and localized suppurative inflammation, are the hallmark of CGD. Pulmonary involvement is especially common, with *Staphylococcus aureus*, *Aspergillus* species, and *Mycobacterium tuberculosis* among the most commonly identified pathogens [15–17]. Radiologic findings often include multiple nodules or mass-like opacities, reflecting chronic rather than acute infection; classic features such as cavitation or halo signs are less typical. Excessive inflammatory responses can also produce granulomatous lesions in the skin, gastrointestinal tract, and urinary tract. These can mimic other conditions, such as pyloric stenosis or food allergies in the gastrointestinal tract, or glomerular diseases such as acute nephritis or IgA nephropathy when involving the urinary system [18].

In the present case, the proband had a history of respiratory tract infection (details unknown) before admission, presenting with fever, occasional cough, and right subcostal pain but without distinctive clinical features. Laboratory testing showed markedly elevated C-reactive protein with only modest leukocytosis, suggesting an atypical inflammatory response. Immunoglobulin concentrations were normal, which helped to exclude other primary immunodeficiencies such as severe combined immunodeficiency, X-linked agammaglobulinemia, hyper-IgM syndrome, and hyper-IgE syndrome.

For suspected CGD, screening tests such as the nitroblue tetrazolium (NBT) reduction assays or flow cytometric respiratory burst evaluation can facilitate rapid diagnosis. However, in this instance, the child's hospitalization was brief and disease progression was fulminant, so neither assay was performed prior to death. The proband's older brother died at age six from an unspecified infection, raising the possibility of undiagnosed CGD within the family. WES ultimately identified a hemizygous *CYBB* variant (c.252G > A; p.Ala84=) in exon 3, with the child's mother confirmed as a carrier.

Management of CGD focuses primarily on preventing and controlling infections. Current recommendations include prophylactic use of recombinant human interferon-γ, trimethoprim–sulfamethoxazole, and itraconazole [19]. Corticosteroids may be administered in cases of significant granulomatous inflammation [20]. Curative options center on immune reconstitution, namely hematopoietic stem cell transplantation or emerging gene therapy approaches [21, 22]. Numerous reports describe successful transplantation outcomes worldwide [23]. For instance, one British cohort of 20 children transplanted between 1998 and 2007 reported an approximately 90% survival rate with normal post-transplant growth and development [24].

Conclusions

This case underscores the critical role of early recognition of CGD and timely molecular diagnosis. If the older brother in this case had undergone genetic testing, it could have guided prenatal diagnosis to either prevent the birth of a child with the same condition or enable early intervention after birth.The identification of specific variants not only guides clinical management but also enables prenatal testing for high-risk families, thereby preventing recurrence of this severe disorder.

Abbreviations

CGD	Chronic Granulomatous Disease
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
G + GM	Fungal Antigens
NGS	Next-Generation Sequencing
PICU	Pediatric Intensive Care Unit
FDP	Fibrin Degradation Products
CPAP	Continuous Positive Airway Pressure
BCG	Bacillus Calmette-Guérin
NBT	The Nitroblue Tetrazolium

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

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Authors' contributions

HL collected the data, wrote the manuscript, analyzed the data, and supervised the study. ZJ participated in the patient's clinical care and collected the data. YQ, GW, and YC participated in the patient's clinical care and collected the data. All authors contributed to the article and approved the submitted version.

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Data availability

The raw sequence data reported in this paper have been deposited in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2025) in National Genomics Data Center (Nucleic Acids Res 2025), China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences (GSA-Human: HRA015837) that are publicly accessible at https://ngdc.cncb.ac.cn/gsa-human.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by Lanzhou University Second Hospital, adhered to the Declaration of Helsinki, Written informed consent to participate in this study was provided by the participants'legal guardian/next of kin.

Consent for publication

Written informed consent was obtained from the minor(s) legal guardian/next of kin, allowing for the publication of this case report and any accompanying images.

Competing interests

The authors declare no competing interests.

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