Novel variants in \textit{CIITA} caused type II bare lymphocyte syndrome: A case report

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Abstract

\textbf{Background:} Type II bare lymphocyte syndrome (BLS II) group A is a rare primary severe immunodeficiency caused by defects in \textit{CIITA}, one of genes encoding transcriptional regulatory factors for MHC II molecules.

\textbf{Objective:} To report a Chinese boy with mutation of \textit{CIITA}.

\textbf{Methods:} By reviewing the clinical data of the child and performing a literature search of BLS II group A.

\textbf{Results:} The patient was presented with persistent pneumonia, chronic diarrhea, urinary tract infection, rash, failure to thrive and special facial characteristics. The patient carried novel mutations in \textit{CIITA} (c.1243delC, p.R415fs*2 and c.3226C>T, p.R1076W) which were identified by next-generation sequencing and confirmed by Sanger sequencing.

\textbf{Conclusion:} This study found novel mutations in the \textit{CIITA} gene of BLS II, which complemented the mutation spectrum and contributed to the diagnosis, treatment, genetic counseling and prenatal diagnosis of BLS II.

\textbf{Key words:} Type II bare lymphocyte syndrome; \textit{CIITA} gene; novel mutations; MHC II; genetic disorder

Introduction

Type II bare lymphocyte Syndrome (BLS II) is a kind of severe primary immunodeficiency which is an autosomal recessive rare heredopathia with clinical symptoms including respiratory and gastrointestinal infections, and liver/biliary tract disease, which was first described in 1979.\textsuperscript{1} Abnormalities in transcription factors, which is essential for the initiation of the transcription of class II major histocompatibility complex (MHC II), would contribute to the occurrence of BLS II, with low CD4\(^+\) cell and absent MHC II expression on lymphocytes.\textsuperscript{2} Four sub-groups of BLS II based on defect type can be categorized into group A, B, C, and D. Group A represents BLS II caused by aberrant class II major histocompatibility complex transactivator (\textit{CIITA}) and makes up about 11\% of all cases of BLS II.\textsuperscript{3} \textit{CIITA} is encoded by the 27-exon gene \textit{CIITA}, located on 16p 13.13, encoding a non-DNA-binding transcription factor composed of 1130 amino acids, encoding an N-terminal acidic domain, a proline-, serine-, and threonine-rich (PST) domain, a GTP-binding site, at least four nuclear localization sequences (NLSs) and leucine-rich regions (LRRs).
which all can bind with factors independently. Studies provide evidence that these domains probably interact with each other and any mutation could affect transcriptional activity. CIITA regulates the expression of MHC class II of T helper cell, forming the basis of the adaptive immune response. Hence, CIITA mutation would cause serious damage to the immune system and severe disorders.

In this report, we present a case of BLS II with novel compound heterozygous variants of CIITA to promote awareness of the disease.

**Report of case**

**Patient**

Here we report a case of BLS II in a 19-month-old male Chinese patient. The patient was born at full term via cesarean section to non-consanguineous Chinese parents with a birth weight at 3500 g. Before birth, the couple had undergone an ectopic pregnancy. No family history of similar diseases existed. He was first referred to the hospital at the age of 9 months due to week-long diarrhea, five days of rash, and three days of cough. Later, urinary tract infection appeared. Laboratory inspection revealed a positive CMV infection in sputum specimen, bacterial infection in urine specimen and lactose intolerance, together with normal CD4+ T cell, increased levels of CD8+ T cell and B cell, inverted CD4/CD8 ratio, decreased IgA and IgG levels and increased IgM levels (Table 1). The patient received symptomatic antibiotic therapy and intravenous immunoglobulin therapy (IVIg). Rash and urinary tract infections alleviated, while diarrhea persisted. Two months later, the boy was admitted again due to severe pneumonia and urinary tract infection. The disease developed later, the boy was admitted again due to severe pneumonia. Acinetobacter baumannii infection. The immunocyte count and level of immunoglobulin remain abnormal. Further diagnosis and genetic tests were implemented. The child presented with chronic diarrhea (frequency of 3 to 4 times a day) and susceptible to respiratory tract infection. No neurological or physical abnormality found. His weight was 7.3 kilograms (< 3 SD) with a head circumference of 44 centimeters (< 2 SD) indicating severe malnutrition. He had pericardial edema, wide and flat nose bridge, protruding ears, and sparse hair (Figure 1A). Considering the patient’s early onset, susceptibility to multiple infections, abnormal immunocyte and immunoglobulin, the patient might suffer from a genetic disease, so high-throughput sequencing was conducted. The patient is preparing for hematopoietic stem cell transplantation.

**Table 1. Immunologic characteristics of the patient**

|                  | 9 mo    | 12 mo   |
|------------------|---------|---------|
| IgG (g/L) (4.09-7.03) | < 1.37  | 5.86    |
| IgA (g/L) (0.21-0.47) | < 0.065 | < 0.066 |
| IgM (g/L) (0.33-0.73) | 4.19    | 1.32    |
| lymphocyte (800-4000/μL, 20-40%) | 14000, 66.4 | 10990, 82.4 |
| CD3+ cell (700-2100/μL, 59-84%) | 9730, 69.52 | 6470, 58.9 |
| CD3+CD4+ cell (300-1400/μL, 31-60%) | 1420, 10.11 | 860, 7.80 |
| CD3+CD8+ cell (200-900/μL, 13-38%) | 7690, 54.92 | 5270, 47.95 |
| CD3 CD16/56+ cell (90-600/μL, 6-27%) | 460, 3.27 | 160, 1.46 |
| CD3 CD19+ cell (100-500/μL, 7-22%) | 2980, 21.28 | 4000, 36.42 |
| CD4+/CD8+ ratio (0.9-3.6) | 0.18    | 0.16    |
| CMV-DNA (sputum) | positive | positive |

Values were obtained at the time of presentation. Reference ranges are in parentheses.

**CIITA genetic testing result**

Genomic DNA of the patient and his parents was extracted from peripheral blood samples using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany). Then next generation sequencing, sanger sequencing, base calling and the sequence read quality assessment were operated. Primers for the amplification of the CIITA gene (GenBank accession No. NM_000246.3) were designed with UCSC ExonPrimer online software. The primers designed for exon 11 were as follows: forward AGTGGTGGCCCTTTGTTGTTG and reverse TTCAAGATGGTTGGTGAAAACC. The primers designed for exon 17~18 were as follows: forward GGAAGGCTGACCAGCATGCAG and reverse CATGATTGGACTCAGGG.

Compound heterozygous variants in CIITA (c.1243delC, p.R415fs*2, c.3226C>T, p.R1076W) were suspected as the possible pathogenic variants through the pipeline described before. Variants were further confirmed using Sanger sequencing in the pedigree. The frameshift variant was detected in the mother at the heterozygous state, located in exon 11 leading to a truncated protein with only 417 amino acids. While the father carried the heterozygous missense variant located in exon 17 on LRRs and caused arginine to change into tryptophan (Figure 1B). Both variants have neither been previously reported and were absent in the Human Genome Mutation Database (HGMD), confirming that the variants are novel.

According to ACMG guideline, the frameshift variant is classified as pathogenic based on evidence PVS1, PM2 and PP4, and the missense mutation is classified as likely pathogenic based on evidence PM1, PM2 and PM3. The above evidences are explained as follows. Neither are included in control databases including Exome Aggregation Consortium, NHLBI Exome Sequencing Project, 1000 Genomes Project, and the Genome Aggregation Database (PM2). CIITA mutations are known to cause disease in a loss-of-function manner.
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(PVS1). And LRRs, being functional domain, are mutational hot spots (PM1). With the addition of corresponding clinical phenotype (PP4) and pathogenicity of maternal variant (PM3), a definite genetic diagnosis can be made.5

(See Sanger sequencing results in Figure 1B)

Figure 1. A. Facial characteristic of the patient. B. Sanger sequencing in CIITA gene. The patient has compound heterozygous mutations in the CIITA gene (c.1243delC, p.R415fs*2 from her mother; c.3226C>T, p.R1076W from her father). C. Distribution of deleterious mutations ever reported on different domains of CIITA. Mutations found in this article are in magenta.

Discussion

BLS II, also known as MHC class II deficiency, is characterized by impaired regulation of the expression of induced and constitutive MHC II. Clinical manifestations of BLS II included early recurrent infections, repeated pneumonia episodes, chronic diarrhea, failure to thrive, and premature death.1 The main feature is the loss of MHC II molecules leading to loss of T lymphocytes, reduced levels of CD4+ T lymphocyte, hypogammaglobulinemia, and impaired antibody production.6

Our patient suffered from a failure to thrive, chronic diarrhea, urinary tract infection, recurrent lung infection, severe pneumonia, ARDS, respiratory failure, and heart failure at the age of 9 months. His phenotype is consistent with the clinical manifestation for BLS II. Laboratory tests reflected normal CD4+/CD8+ ratio, reduced levels of IgA and IgG, increased IgM, and infection with CMV and Acinetobacter baumannii. Following regular antibiotic therapy and IVIg, the level of IgG returned to normal; even though the condition was unstable. Genetic testing was conducted, and the result showed our patient carried novel compound heterozygous variants in CIITA (c.1243delC, p.R415fs*2 and c.3226C>T, p.R1076W).

Based on a review of reported cases, along with a case report in Chinese by Chen et al, there have been only 16 BLS II patients with CIITA mutations (Table SI), including 6 missense, 5 nonsense, 5 deletions and 1 splice site mutation (Figure 1C).7-19 The average onset age was 9.6 months except special cases with no symptoms or extremely late age of onset.19
The immunologic characteristics of the disease have heterogeneity. Normal CD4+ T cell count and high level IgM in our patient are quite distinct but each has been reported with symptoms. There has been only one Chinese patient reported with high level IgM. Hence our report supplements phenotype spectrum and suggests Chinese patient might be more likely to have increasing immunoglobulins.

So far, facial characteristics have only been reported in one case including hypertelorism, and sparse, coarse scalp hair. Yet, this patient presented with sparse hair, epicanthus, wide and flat nose bridge, nostril anteversion, high columella, deep and flat philtrum, cupid lip, and protruding ears (Figure 1A). This case shows consistent and more detailed facial characteristics. With two in eighteen patients having facial distinction, the fact CIITA mutation might affect the facial appearance might be helpful during clinical diagnosis.

BLS II group A patients showed poor prognosis, with the average age of death being four years. The only possible cure is hematopoietic stem cell transplantation (HSCT) despite only 60% of success rate. Thus, acute infection and complications should be actively treated to alleviate relevant clinical symptoms. Intravenous anti-infective drugs, intravenous gamma globulin, parenteral nutrition, and prophylactic use of antibiotics should be taken into consideration as treatment.

In summary, this article is to report a rare case of BLS II with novel pathogenic variants which could enrich the genetic and phenotypic spectrum for this disorder. A literature review of the previously reported patients revealed more heterogeneity. Normal CD4+ T cell count and high level IgM in our patient are quite distinct but each has been reported with symptoms.

Competing interests
The authors declare that they have no conflict of interests

Authors’ contributions
- YZ critically drafted and revised the manuscript, and reviewed the literature for data on other reported patients suffering from BLS II.
- LY and YX assessed the clinical manifestation of the patient and collected the raw data from our hospital work system.
- JW and RY analysed data generated by next generation sequencing, found the variants, judged the pathogenicity and reviewed the manuscript.
- YQ, CH, JZ and TY operated Sanger sequencing to confirm the variants. All authors have read and approved the manuscript.

Acknowledgments
We thank all the members of the family for their participation in this study.

Literature review
All of the literature for previously published CIITA mutations (from 1989 to 2019) was retrieved from PubMed and Human Genome Mutation Database (HGMD), together with a case report in Chinese by Chen et al. (Chen et al., 2018). The clinical characteristics and mutation spectrum of the CIITA gene were then summarized.

Supplementary Material (websites utilized)
1. 1000 Genomes Project
http://www.1000genomes.org
2. Exome Aggregation Consortium
http://exac.broadinstitute.org
3. Genome Aggregation Database
http://gnomad-old.broadinstitute.org
4. Human Genome Mutation Database
http://www.hgmd.cf.ac.uk
5. NHLBI Exome Sequencing Project
http://evs.gs.washington.edu/EVS
6. UCSC ExonPrimer
http://genome.ucsc.edu/index.html

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| Sex       | Sibling          | Age of onset | Age at diagnosis | Recurrent respiratory tract infection | Candidiasis | Chronic diarrhea | Failure to thrive | Malignation | Recurrence of this illness | Septicemia | Organism isolated (source) | Other manifestations | Status                                                                 |
|-----------|------------------|--------------|------------------|---------------------------------------|-------------|------------------|------------------|-------------|--------------------------|------------|----------------------------|---------------------|------------------------------------------------------------------------|
| Male      | NA               | 5 mo         | 3.5Y             | +                                     | +           | +                | +                | +           | -                        | -          | Candida albicans           | -                   | alive at 7 Y on high-dose IVIG                                     |
| Female    | NA               | 3 mo         | 3 Y              | +                                     | -           | +                | -                | -           | NA                       | -          | NA                        | -                   | alive at 3 Y prepared for bone marrow transplantation                   |
| Male      | -                | -             | -                | -                                     | -           | -                | -                | -           | NA                       | -          | NA                        | -                   | died because of multiple bacterial infections in early thirties        |
| Female    | NA               | 15 Y         | -                | -                                     | -           | -                | -                | -           | +                        | -          | S. pneumonia/Haemophilus influenzae                                   | -                   | healthy at 24 Y/No treatment                                         |
| Male      | NA               | 12 Y         | -                | +                                     | -           | -                | -                | +           | NA                       | -          | +                         | -                   | alive at 22 Y/IVIG and antibiotics (occasional)                        |
| Female    | NA               | 11 Y         | -                | +                                     | -           | -                | -                | +           | -                        | NA         | +                         | -                   | alive at 21 Y/IVIG and antibiotics                                     |
| Male      | NA               | 5 Y           | -                | +                                     | +           | +                | +                | +           | -                        | NA         | Na                        | -                   | died after transplantation                                             |
| Female    | NA               | 5 Y           | -                | +                                     | +           | +                | +                | +           | -                        | -          | Cyto megalovirus           | -                   | alive at 5 Y/IVIG and antibiotics                                     |
| Male      | NA               | 15 mo         | 5 Y              | +                                     | +           | +                | +                | +           | -                        | +          | Mycobacterium tuberculosis/ C. albicans                              | +                   | chronic rhinorrhea/recurrent oral ulcers/skin abscesses/vaginitis/cervicitis                             |
| Female    | NA               | 6 mo         | 9 Y              | +                                     | -           | -                | +                | -           | -                        | +          | Pneumocystis jirovecii/H. influenza virus/ Human respiratory syncytial virus | +                   | Pneumocystis jirovecii/ H. influenza virus/ Human respiratory syncytial virus |
| Male      | NA               | 5 mo         | 5.5Y             | +                                     | +           | +                | +                | -           | -                        | -          | Na                        | -                   | alive at 14 Y/IVIG/ antimerosal prophylaxis/ granulocyte colony stimula- |
| Female    | NA               | 6 mo         | 12 Y             | +                                     | +           | +                | +                | +           | -                        | -          | Na                        | -                   | alive at 6 mo/Cause of death/ pneumonia                              |
| Male      | NA               | 4 mo         | 7 mo             | +                                     | -           | -                | +                | -           | -                        | -          | -                        | -                   | Died at 4 mo/Cause of death/ pneumonia                                |
| Female    | NA               | 6 mo         | 12 mo            | +                                     | +           | +                | +                | +           | -                        | -          | -                        | -                   | Died at 8 Y/Cause of infection                                        |
| Male      | NA               | 1 Y           | 8 Y              | +                                     | -           | -                | +                | +           | +                        | -          | Epstein-Barr virus/Fungus                                         | +                   | sinusitis/acute respiratory distress syndrome and heart failure        |
| Female    | NA               | 2 mos         | 3 mo             | +                                     | +           | +                | +                | +           | -                        | +          | Na                        | -                   | died at 3 mos because of sepsis                                       |
| Male      | NA               | 9 mos         | 19 mos            | +                                     | +           | +                | +                | +           | +                        | -          | Cytomegalovirus/A. meobacter haemolyticum                            | +                   | respiratory tract infection/ atrial septal defect/ renal failure/ and heart failure |

**Table S1. Clinical phenotypes and genetic features of BLS II patients with CIITA mutations reported**
Table S2. Immunologic parameters, domains affected and ethnicity of BLS II patients with CIITA mutations reported

|            | IgG     | IgA     | IgM     | Lymphocyte | CD3+ T Cells | CD4+ T Cells | CD4+/CD8+ ratio | CD4+ CD56- Na | CD56+ B Cells | HLA-DR expression on monocytes, B cells | affected domains or second structures | Ethnicity          |
|------------|---------|---------|---------|------------|--------------|--------------|----------------|---------------|---------------|-----------------------------------------|--------------------------------------|--------------------|
| Steinle et al. 1993 | normal  | normal  | normal  | normal      | NA           | NA           | 0.31 reversed   | NA            | NA            | undetectable                           | NLS3                   | NA                 |
| Bontron et al. 1997 | hypogammaglobulinemia | NA   | NA     | NA         | NA           | NA           | NA             | NA            | NA            | undetectable                           | NLS2/ GTP-binding site/NLS3/ leucine-rich regions | Austrian            |
| Quan et al. 1999 | NA      | NA      | NA      | NA         | NA           | NA           | NA             | NA            | NA            | undetectable                           | beta-sheet             | NA                 |
| Peijnenburg et al. 2000 | NA   | NA      | NA      | NA         | NA           | NA           | NA             | NA            | NA            | undetectable                           | leucine-rich regions    | NA                 |
| Wozniak et al. 2001 | SaE     | normal  | normal  | normal      | normal       | normal       | normal         | NA            | normal         | undetectable                           | defective              | GTP binding site  | NA                  |
|             | SaM     | normal  | very low level | normal     | normal       | low level    | high level     | NA            | normal         | undetectable                           | defective              | GTP binding site  | NA                  |
|             | SaA     | low level | very low level | normal     | high level   | high level   | high level     | NA            | normal         | undetectable                           | defective              | GTP binding site  | NA                  |
| Dziembowska et al. 2002 | SP   | very low level | very low level | low level   | NA           | normal low level | low level | low level | NA            | NA            | undetectable                           | leucine-rich regions    | NA                 |
|             | RC      | very low level | very low level | very low level | NA           | normal       | normal         | NA            | NA            | undetectable                           | leucine-rich regions    | NA                 |
| Dimitriou et al. 2014 | normal  | very low level | normal    | low level   | very low level | low level    | 0.5 reversed   | normal         | high level     | undetectable                           | leucine-rich regions    | Mexican-American                  |
| Ahmed et al. 2015 | very low level | very low level | low level | normal      | low level    | very low level | normal      | < 0.1 reversed | high level     | undetectable                           | PST domain/NLS2/GTP binding site/NLS3/leucine-rich regions | Hispanic               |
| Yu et al. 2016 | NA      | NA      | low level | NA         | NA           | very low level | low level     | NA            | high level    | undetectable or defective               | GTP binding site         | NA                 |
| al-Mousa et al. 2016 | NA    | NA      | NA      | NA         | NA           | NA           | NA             | NA            | NA            | undetectable                           | leucine-rich regions    | NA                 |
| Altamir et al. 2018 | very low level | normal   | normal   | normal      | very low level | high level   | NA            | normal         | normal         | undetectable                           | NLS3/leucine-rich regions | NA                 |
| El Hawary et al. 2019 | very low level | very low level | low level | normal      | low level    | very low level | normal      | NA            | high level    | undetectable                           | PST domain/NLS3/leucine-rich regions | Egyptian              |
| Chen et al. 2018 | P1      | high level | high level | high level  | NA           | high level   | very low level | high level     | 0.19 reversed | NA            | defective                            | PST domain         | Chinese            |
|             | P2      | very low level | normal   | normal      | NA           | high level   | 0.11 reversed  | normal         | high level     | NA            | GTP binding site/NLS3/leucine-rich regions | Chinese               |
| This report | low level | very low level | high level | high level  | NA           | normal       | 0.18 reversed  | normal         | high level     | NA            | GTP binding site/NLS3/leucine-rich regions | Chinese               |