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CASE REPORT

Novel variants in *CIITA* caused type II bare lymphocyte syndrome: A case report

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Abstract

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

Objective: To report a Chinese boy with mutation of *CIITA*.

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

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 *CIITA* (c.1243delC, p.R415fs*2 and c.3226C>T, p.R1076W) which were identified by next-generation sequencing and confirmed by Sanger sequencing.

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

Key words: Type II bare lymphocyte syndrome; *CIITA* gene; novel mutations; MHC II; genetic disorder

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List of abbreviations:

BLS II	Type II Bare Lymphocyte Syndrome
MHC II	Class II Major Histocompatibility Complex
CIITA	Class II Major Histocompatibility Complex Transactivator
IVIg	Intravenous Immunoglobulin Therapy
ARDS	Acute Respiratory Distress Syndrome
ACMG	American College of Medical Genetics
HGMD	Human Genome Mutation Database
PST	Proline-, Serine-, and Threonine-rich (PST) domain
NLSs	Nuclear Localization Sequences

List of abbreviations (Continued):

LRRs	Leucine-Rich Repeats
HSCT	Hematopoietic Stem Cell Transplantation
TREC	T-cell Receptor Excision Circles

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.[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.[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 (*CIITA*) and makes up about 11% of all cases of BLS II.[3]

CIITA is encoded by the 27-exon gene *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.[4] Studies provide evidence that these domains probably interact with each other and any mutation could affect transcriptional activity.[4] *CIITA* regulates the expression of MHC class II of T helper cell, forming the basis of the adaptive immune response.[4] 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 for not receiving advised regular IVIg. The disease developed into acute respiratory distress syndrome (ARDS), followed by respiratory failure and heart failure. Mechanical ventilation, anti-infective treatment, and IVIg were utilized. Review of flow cytometry and humoral immunity showed normal $CD4^+$ T cell, high level of $CD8^+$ T cell and B lymphocyte.

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.

The level of IgG and IgM returned to normal. CT scan indicates bronchopneumonia and a smaller thymus comparing with normal. Patient recovered discharged but continued to receive regular IVIg therapy for the next 6 months. The patient continued to suffer recurrent lung infections, chronic diarrhea, CMV infection and failure to thrive. In the meantime, IgM level increased again with normal IgG. When the patient reached 19 months, he experienced respiratory failure and heart failure again, but was resuscitated. Sputum culture was positive for *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 periocular edema, wide and flat nose bridge, protruding ears, and sparse hair (**Figure 1A**). Considering the patient's early onset, susceptibleness 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.

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 AGTGCTGGCCTTGTGGTG and reverse TTCAAGATGTGGCTGAAAACC. The primers designed for exon 17~18 were as follows: forward GGAAGGCTGACCAT GCAC and reverse CATGATTTGAGCTCCGGG.

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.[5] 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

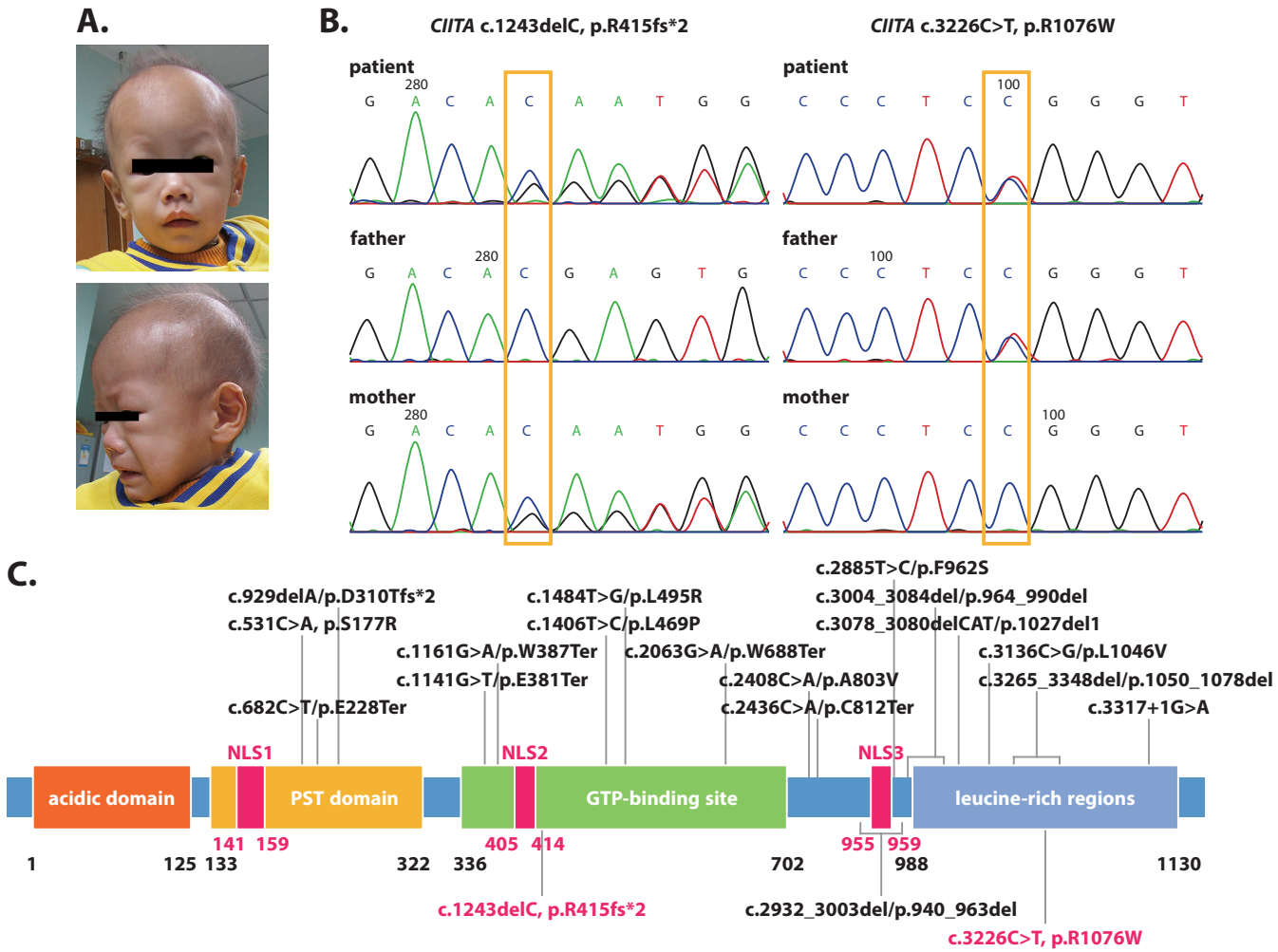

Figure 1. A. Facial characteristic of the patient. B. Sanger sequencing in CIITA gene. The patient has compound heterozygous mutations in the *CIITA* gene (c.1243delC, p.R415fs*2 from her mother; c.3226G>A, p.R1076W from her father). C. Distribution of deleterious mutations ever reported on different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

(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**)

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 $CD4^+$ T cell, increased $CD8^+$ T cell and B cell, inverted $CD4^+/CD8^+$ 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).

The frameshift variant is classified as pathogenic, affecting the function of *CIITA*, producing a premature protein without a complete GTP-binding site, NLS, and LRRs. The missense mutation located in the LRRs is classified as likely pathogenic. Although we could not test the expression density of HLA-DR or DQ on B cells or monocytes, the diagnosis of BLS II could be made through a combination of the patient's clinical manifestations and gene mutations.

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.[7-19]

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.[7-18] There has been only one Chinese patient reported with high level IgM.[19] Hence our report supplements phenotype spectrum and suggests Chinese patient might be more likely to have increasing immunoglobins.

So far, facial characteristics have only been reported in one case including hypertelorism, and sparse, coarse scalp hair.[7] 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 has 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.[20] 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 genotypic and phenotypic spectrum for this disorder. A literature review of the previously reported patients revealed more heterogeneous immunologic characteristics and specific facial characteristics that were linked to this rare condition.

Conflict of Interest

The authors declare no conflict of interest.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at Shanghai Children's Medical Center (SCMCIRB-Y2019021) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the parents of the participant included in the study.

Consent for publication

Written informed consent was obtained from the patient's father for publication of this research.

Availability of data and material

The datasets (whole-exome sequencing and Sanger sequencing files) used and/or analyzed during the current study are available from the corresponding author on reasonable request.

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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

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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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Table S1. Clinical phenotypes and genetic features of BLS II patients with *CIITA* mutations reported

		Sex	Consanguinity	affected siblings	Age of onset	Age at diagnosis	Recurrent respiratory tract infection	Candidiasis	Chronic diarrhea	Failure to thrive	Malnutrition	Recurrent otitis media	Septicemia	Organism isolated (source)	Special facial characteristics	Other manifestations	Status	Mutation
Steimle et al. 1993		♀	NA	-	5 mo	3.5 Y	+	+	+	+	+	+	-	*Candida albicans*	-	-	alive at 7 Y/on high-dose IVIg	Homo c.2932_3003del/ p.940_963del
Bontron et al. 1997		♂	-	-	3 mo	3 Y	+	-	-	+	+	-	-	NA	-	-	alive at 3 Y/prepared for bone marrow transplantation	c.1141G>T/ p.E381Ter.3317 +1G>A
Quan et al. 1999		♂	NA	-	in twenties	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	died because of multiple bacterial infections in early thirties	Homo c.2885T>C/ p.F962S
Peijnenburg et al. 2000		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Homo c.3265_3348del/ p.1050_1078del
Wiszniewski et al. 2001	SaE	♀	-	2♀	-	15 Y	-	-	-	-	-	-	-	*Streptococcus pneumoiae/ Haemophilus influenzae*	-	-	healthy at 24 Y/No treatment	Homo c.1406T>C/p.L469P
	SaM	♀	-	1♀	3 mo	12 Y	+	-	-	-	-	-	+	NA	-	asymptomatic from 9 to 12 Y	alive at 22 Y/on IVIg and Antibiotics (occasional)	Homo c.1406T>C/p.L469P
	SaA	♀	-	1♀	NA	11 Y	+	-	-	-	-	-	-	Herpes simplex virus	-	short stature/hepatosplenomegaly/swelling lymph nodes/atrial septal defect	alive at 21 Y/on IVIg and antibiotics	Homo c.1406T>C/p.L469P
Dziembowska et al. 2002	SP	♀	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	died after transplantation	c.2063G>A/p.W688Ter paternal allel lost
	RC	♂	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Cytomegalovirus	NA	NA	died because of infection	c.3078_3080delCAT/ p.1027delI c.3004_3084del/ p.964_990del
Dimitrova et al. 2014		♂	-	-	15 mo	5 Y	+	+	+	+	-	+	+	*Mycobacterium tuberculosis/ Candida albicans*	+	chronic rhinorrhea/recurrent oral ulcers/skin abscesses/symptommatic varicella after vaccine administration/ recurrent polyarthritis/ chronic sinusitis/subcutaneous skin nodules with eczematoid lesions/mediastinal mass	alive at 5 Y/on IVIg and antibiotic prophylaxis	Homo c.3317+1G>A
Ahmed et al. 2015		♀	+	1 died in infancy from pneumonia	6 mo	9 Y	+	-	-	+	-	-	-	*Pneumocystis jiroveci*/Rhinovirus/Human respiratory syncytial virus	-	profound neutropenia/ renal tubular acidosis and anti-thyroid antibodies	alive at 14 Y/on IVIg/ antimicrobial prophylaxis/ granulocyte colony stimulating factor	Homo c.682C>T/p. E228Ter
Yu et al. 2016		♂	NA	1♀ died after bone marrow transplantation	5 mo	5.5 mo	+	NA	NA	NA	NA	NA	NA	*Pneumocystis jirovecii*	NA	NA	NA	c.1484T>G/p.L495R One copy loss of the whole gene
al-mousa et al. 2016		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Homo c.3136C>G/p. L1046V
Aluri et al. 2018		♂	-	-	4 mo	7 mo	-	-	-	+	-	-	-	*Chryseobacterium indologenes*	-	acute respiratory distress syndrome	Alive/on IVIg prophylaxis	Homo c.2436C>A/p. C812Ter
El Hawary et al. 2019		♂	+	-	6 mo	12 mo	+	+	+	+	-	-	-	-	-	-	Died at 16 mo/Cause of death unclear	Homo c.929delA/p. Asp310Tfs*2
Chen et al. 2018	P1	♂	NA	1♀ died after Varicella vaccination	4 Y	8 Y	+	-	-	-	-	+	+	Epstein-Barr virus/Fungus	-	sinusitis/acute respiratory distress syndrome/herpes/ hepatomegaly, slightly hard texture/double kidney enlargement with damage	died at 8 Y because of infection	c.531C>A/p.S177R c.2408C>A/p.A803V
	P2	♂	NA	1 natural abortion	2 mo	3 mo	+	-	+	-	-	-	+	NA	-	Rash	died at 3 mo because of sepsis	Homo c.1161G>A/p. W387Ter
This report		♂	-	-	9 mo	19 mo	+	-	+	+	+	-	+	*Cytomegalovirus/ Acinetobacter baumannii*	+	rash/urinary tract infection/ acute respiratory distress syndrome/respiratory failure and heart failure	Alive at 20 mo/on IVIg prophylaxis	c.1243delC,p.R415fs*2 c.3226C>T, p.R1076W

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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	CD8⁺ T Cells	CD4⁺/CD8⁺ ratio	CD16⁺, CD56⁺ Nk	CD19⁺ B Cells	HLA-DR expression on monocytes, B cells	affected domains or second structures	Ethnicity
Steimle et al. 1993		normal	normal	normal	normal	normal	NA	NA	0.31 reversed	NA	normal	undetectable	NLS3	NA
Bontron et al. 1997		hypogammaglobulinemia			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	NA	undetectable	β-sheet	NA
Peijnenburg et al. 2000		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	undetectable	leucine-rich regions	NA
Wiszniewski et al. 2001	SaE	normal	normal	normal	normal	normal	normal	normal	NA	normal	normal	defective	GTP-binding site	NA
	SaM	normal	very low level	normal	normal	normal	low level	high level	NA	normal	normal	defective	GTP-binding site	NA
	SaA	low level	very low level	normal	high level	high level	normal	high level	NA	normal	normal	defective	GTP-binding site	NA
Dziembowska et al. 2002	SP	very low level	very low level	low level	NA	NA	very low level	low level	NA	NA	NA	undetectable	GTP-binding site/NLS3/ leucine-rich regions	NA
	RC	very low level	very low level	very low level	NA	NA	normal	normal	NA	NA	NA	undetectable	leucine-rich regions	NA
Dimitrova 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 and Persian
Ahmed et al. 2015		very low level	very low level	low level	normal	low level	very low level	normal	< 0.1 reversed	very low level	high level	undetectable	PST domain/NLS2/ GTP-binding site/NLS3/ leucine-rich regions	Hispanic
Yu et al. 2016		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	undetectable or defective	GTP-binding site	NA
al-mousa et al. 2016		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	undetectable	leucine-rich regions	NA
Aluri et al. 2018		very low level	normal	normal	normal	normal	very low level	high level	NA	normal	normal	undetectable	NLS3/leucine-rich regions	Indian
El Hawary et al. 2019		very low level	very low level	low level	normal	low level	very low level	normal	NA	NA	high level	undetectable	PST domain/NLS2/ GTP-binding site/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	NA	defective	PST domain	Chinese
	P2	very low level	normal	normal	NA	low level	very low level	high level	0.1 reversed	NA	NA	NA	NLS2/GTP-binding site/NLS3/leucine-rich regions	Chinese
This report		low level	very low level	high level	NA	high level	normal	high level	0.18 reversed	normal	high level	NA	GTP-binding site/ leucine-rich regions	Chinese