Journal of Clinical Immunology (2019) 39:309–315
https://doi.org/10.1007/s10875-019-00617-4

ORIGINAL ARTICLE

Report of a Chinese Cohort with Leukocyte Adhesion Deficiency-I and Four Novel Mutations

Bijun Sun[1] · Qiuyu Chen[1] · Xiaolong Dong[1] · Danru Liu[1] · Jia Hou[1] · Wenjie Wang[1] · Wenjing Ying[1] · Xiaoying Hui[1] · Qinhua Zhou[1] · Haili Yao[1] · Jinqiao Sun[1] · Xiaochuan Wang[1]

Received: 28 December 2018 / Accepted: 18 March 2019 / Published online: 27 March 2019

Abstract

Purpose We aimed to report the characteristics of leukocyte adhesion deficiency-I (LAD-I) and four novel mutations in the *ITGB2* gene in a Chinese cohort.

Methods Seven patients with LAD-I were reported in our study. Clinical manifestations and immunological phenotypes were reviewed. The expression of CD18 was detected by flow cytometry. Next-generation sequencing (NGS) and Sanger sequencing were performed to identify gene mutations.

Results The mean onset age of all the patients was 1.3 months. Recurrent bacterial infections of the skin and lungs were the most common symptoms. Most patients (6/7) had delayed cord separation. The number of white blood cells (WBC) was increased significantly, except that two patients had a mild increase in the number of WBC during infection-free periods. The expression of CD18 was very low in all patients. Homozygous or compound heterozygous mutations in the *ITGB2* gene were identified in each patient. Four mutations were novel, including c.1794dupC (p.N599Qfs*93), c.1788C>A (p.C596X), c.841-849del9, and c.741+1delG. Two patients had large deletions of the *ITGB2* gene. Five patients were cured by hematopoietic stem cell transplantation (HSCT).

Conclusions This study reported the clinical and molecular characteristics of a Chinese patient cohort. It is helpful in understanding the current status of the disease in China.

Keywords Leukocyte adhesion deficiency type I · genetic testing · *ITGB2* gene · immunodeficiency · novel mutation

Introduction

Leukocyte adhesion deficiency (LAD) is an autosomal recessive primary immunodeficiency that has been divided into three types: LAD-I, II, and III, in which LAD-I is the most common (prevalence of 1 in 1,000,000 live births) [1]. The distinct features of LAD patients are recurrent bacterial and fungal infections, omphalitis with delayed umbilical stump separation, significant leukocytosis especially neutrophilia during infection periods, impaired pus formation, and delayed traumatic or surgical wound healing [2, 3].

LAD-I is caused by integrin beta-2 subunit (*ITGB2*) gene deficiency, which results in the decreased expression or function of CD18, the β2 subunit of leukocyte β2 integrins, and leads to severely impaired leukocyte adhesion to the vascular wall and leukocyte migration to sites of inflammation [4]. Flow cytometry is considered a useful tool for rapid diagnosis of the disease. The study of CD18 and CD11 (a, b, c) expression patterns in peripheral blood leukocytes helps to distinguish different phenotypes of LAD-I. In general, patients with ≥ 2% CD18 expression tend to have a less severe infection and often survive until adulthood, whereas < 2% CD18 expression often results in death in infancy [5–8]. Different types of mutations in *ITGB2* gene have been reported, such as deletion, truncation, substitution, frameshifts, and intronic mutations, of which substitution and frameshift are the most frequent [9]. Thus, detection of *ITGB2* gene mutation is routinely used for diagnosis of the disease.

Bijun Sun and Qiuyu Chen contributed equally to this work.

✉ Jinqiao Sun
jinqiaosun@fudan.edu.cn

✉ Xiaochuan Wang
xchwang@shmu.edu.cn

[1] Department of Clinical Immunology, Children's Hospital of Fudan University, 399 Wanyuan Road, Shanghai 201102, China

Although the disease has been known for nearly 40 years, only a few cases were reported in China until now [10–13]. In this study, we reported the clinical and genetic characteristics of seven Chinese patients with LAD-I.

Methods

This study was approved by the Ethics Committee of the Children's Hospital of Fudan University. Written informed consent was obtained from the parents of all patients.

Patients

Children with LAD-I admitted to our hospital between January 2016 and November 2018 were included in this study. LAD-I was diagnosed by clinical manifestations, laboratory findings, and genetic data. Relevant information was collected and summarized, including gender, age, family history, infection symptoms, treatment, and prognosis.

Routine Immune Function Evaluation

Routine blood counts and immunological function analyses were performed. We used nephelometry to detect immunoglobulins, including IgG, IgA, and IgM as previously reported [14], while lymphocyte subsets were measured by flow cytometry (Becton Dickinson, Franklin Lakes, NJ, USA).

Expression of CD18

Heparin sodium–anticoagulated blood (approximately 1 ml) was collected from the patients and their parents. The expression of CD18 on peripheral blood neutrophils was detected by using a FACSCalibur flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). PE anti-human CD18 and isotype-matched control antibodies (BD Biosciences) were added to the reaction system for staining, followed by red blood cell lysis, and washing twice with PBS. The analysis was performed using FACSDiva software (BD Biosciences).

Gene Analysis

Genomic DNA was extracted from the EDTA-anticoagulated blood of patients and their parents by the QIAmp® DNA Blood Mini Kit (Qiagen, Hilden, Germany). The concentration and quantity of the DNA samples were measured using a NanoDrop ultraviolet spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) and then prepared for next-generation sequencing by panel, which included all previously reported immunodeficiency genes.

In accordance with the instructions of the SureSelect Human All Exon Kit, the genomic DNA underwent ultrasonic fragmentation, end repair, adapter connection, and hybridization. The captured DNA library was sequenced on the Illumina HiSeq 2000 platform (Illumina, San Diego, CA). The raw data were converted to a VCF file containing the basic information for the mutation sites through splicing and comparison. We completed the variation annotation by using ANNOVAR and VEP software. The annotation of the mutation frequency referred to databases, including the 1000 Genomes Project, the ExAC browser, and internal databases. Mutation predictions were performed using SIFT, PolyPhen-2, and MutationTaster software. Deletion was identified by NGS coverage depth analysis [15], and the point mutation was confirmed by Sanger sequencing.

Results

Clinical Manifestations

Overview

Seven LAD-I patients (four females, three males) were diagnosed during the past 3 years. None of the patients were consanguineous marriages. The mean age of onset was 1.3 months (range, 4 days–3 months), and four patients presented their first clinical manifestations during the neonatal period. However, the age of diagnosis of the seven patients was about 2 years old. Patient 1 (P1) had a positive family history. His older sister died at the age of 5 months due to right orbital cellulitis and *Pseudomonas aeruginosa* sepsis, but whether she had LAD-I was unclear. P5 developed initial symptoms at 3 months of age but was not diagnosed definitively until she was 10 years old. The mother of P5 had two previous pregnancies that showed embryo dysplasia. The umbilical cord separation was delayed (after 14 days) in six patients. The characteristics of these patients are summarized in Table 1.

Infection Characteristics

Infections were the most common clinical signs, varying in severity. During the neonatal period, two patients had pneumonia and one had omphalitis. The other affected children often first presented with recurrent fever of unknown cause shortly after birth. Subsequent follow-up of these patients revealed that five patients were diagnosed with sepsis accompanied by significant increases in blood inflammatory markers. Two cases mainly manifested as repeated gingivitis with age, while one patient experienced oral and rectal ulcers that were misdiagnosed as "Behcet's syndrome" by local hospital. P7 had difficult healing after trauma mainly due to infection. Surgical treatment was performed in three patients, two of whom developed perianal skin infections and then underwent incision and debridement of abscesses. P1 underwent surgery

Table 1 Clinical characteristics of LAD-I patients

	P1	P2	P3	P4	P5	P6	P7
Age at onset	15 days	2 months	1 month	15 months	3 months	4 days	2 months
Age of diagnosis	4 months	22 months	6 months	12 months	10 years	5 months	21 months
Sex	M	F	M	F	F	M	F
Family history	Yes	No	No	No	Yes	No	No
Cord separation	15 days	1 month	7 days	20 days	1 month	18 days	2 months
Clinical presentation	Recurrent fever, diarrhea, sepsis, omphalitis, urachal fistula, ileus, pneumonia, hypersplenism	Recurrent fever, papulopustule, perianal abscess	Recurrent fever, pneumonia, sepsis	Pneumonia, sepsis, diarrhea, otitis media, pneumonia, malnutrition	Pneumonia, gingivitis, perianal abscess, otitis media, pneumonia, rectal ulcers, epifolliculitis	Omphalitis, pneumonia, sepsis, mycotic stomatitis	Hypersplenism, oral aphthous, gingivitis, sepsis, pneumonia, skin infections
Operation History	Exploratory laparotomy	Abscess incision	No	No	Abscess debridement	No	No
Pathogenic microorganism	Sputamentum: *Enterobacter aerogenes*, *Stenotrophomonas maltophilia*; blood: *Candida parapsilosis*, CMV	Perianal abscess: *Enterococcus faecium*	Negative	Urine: *Enterococcus faecium*	Sputamentum: *Pseudomonas aeruginosa*; excrement: yeast-like fungus	Sputamentum: *Staphylococcus aureus*; blood: CMV	Negative
Min WBC*10^9/L	17.6	18.3	14.9	19.1	11	21.5	10.7
Max WBC*10^9/L	133	88	66.6	69.5	52.6	76.9	82.8
CD18 expression %	2.4	3.6	3.4	2.5	0.8	6.5	0.7
Treatment	UCBSCT	UCBSCT	UCBSCT	UCBSCT	UCBSCT	Anti-infection	Anti-infection
Follow-up	Alive, 33 months	Alive, 47 months	Alive, 15 months	Alive, 17 months	Alive, 11 years	Lost	Alive, 41 months

M, male; *F*, female; *CMV*, *Cytomegalovirus*; *Min*, minimum; *Max*, maximum; *UCBSCT*, umbilical cord blood stem cell transplantation

for urachal fistula and intestinal obstruction. Postoperative wound healing was slow in these patients.

The patients were at high risk for bacterial and fungal infections. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecium*, and *Candida parapsilosis* were usually detected in the blood or secretions from these patients by culture. In addition, two of seven patients had *Cytomegalovirus* (CMV) infections confirmed by CMV antibodies and CMV DNA detection, and these patients recovered with effective ganciclovir therapy.

In the absence of infection, these patients had persistent leukocytosis ranging from 10.7 to 21.5 × 10^9/L (median, 17.6 × 10^9/L), but no specific morphological changes were found. When the patients were infected, the WBC was significantly higher, especially neutrophilia, which returned to baseline levels after aggressive antibiotic treatment.

Immune Function Evaluation

No obvious abnormalities were found in the routine assessment of immune function, including Ig and lymphocyte subsets. A significant defect in CD18 expression was found in all of the affected children compared to normal controls. The expression levels of CD18 were varied from 0.7 to 6.5% (Table 1). The results of one representative patient are shown in Fig. 1.

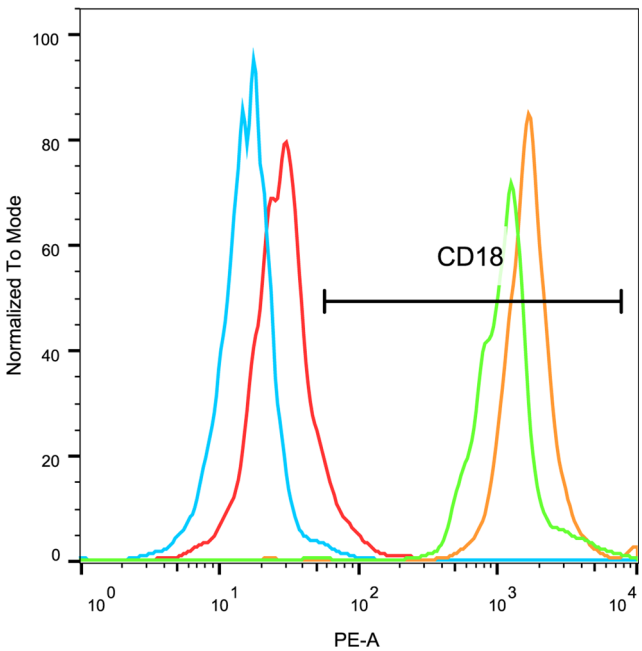

Fig. 1 The expression of CD18 in one typical patient and her healthy parents by flow cytometry. Histogram showing expression of CD18 on neutrophils: Absent expression of CD18 in patient (blue) and normal expression of CD18 in her mother (green) and father (orange), as compared to the isotype-matched control (red). P5: Patient 5. M: mother of P5. F: father of P5

Genetic Characteristics

The mutations of the *ITGB2* gene were identified in all seven cases. Only one patient had homozygous mutation, and the other six were compound heterozygous mutation. All of their parents were heterozygous mutation carriers, except the mother of P1 with no mutation. Previously reported mutations were found, including one splice site, one nonsense, and five missense mutations. Four novel mutations were detected, including c.1794dupC (p.N599Qfs*93), c.1788C>A (p.C596X), c.841-849del9, and c.741+1delG (Table 2). In particular, the data analysis revealed a large chromosomal deletion in P4 and P7, including a whole *ITGB2* gene deletion and an exon 2–exon 8 deletion, respectively. The compound heterozygous mutations of P7 are presented in Fig. 2.

Treatment

Five patients received umbilical cord blood stem cell transplantation (UCBSCT) generally at 5.4 ± 3.4 months after diagnosis and all patients survived. P1 was followed-up for the longest time until 2 years after transplantation and was in good health condition without any complication.

Discussion

LAD is one kind of classical primary immunodeficiency disease. It was first reported by Hayward AR et al. [16] in 1979, and the molecular defects were found in 1984 [17]. LAD-I affects approximately 1 per 1,000,000 live births with no described racial or ethnic predilection [1]. In China, the total number of newborns is approximately 17,000,000 per year. However, there has been a lack of reports of Chinese patients until now, indicating that many patients were misdiagnosis. Moreover, the median age of onset of all patients was 1.3 months and the age at diagnosis was often within 2 years old in our study. The diagnosis was significantly delayed. Although all patients had recurrent infection and were treated in local hospital, no one was told that he/she had LAD-I before they transferred to our hospital. The results suggest that many doctors do not know the disease in China.

LAD-I is a severe disease that often manifests early in life as recurrent bacterial and fungal infections with a reduced inflammatory response and no pus formation [2]. In this study, pneumonia and omphalitis were presented in patients during the neonatal period. All of the patients had developed recurrent infections, including pneumonia, sepsis, skin infection especially perianal infection, otitis media, periodontitis, gastrointestinal ulcer, and diarrhea. Several cases with severe periodontitis have been reported in LAD-I patients [18, 19]. Oral manifestations have been recorded in patients mostly older than 1 year [3, 20, 21]. Periodontitis occurred in two

Table 2 Mutations of ITGB2 gene identified in patients

Patients	Zygosity	Exon/Intron	Mutation	Amino acid	Source of variation	Novelty	Affected domain
P1	Homozygous	Exon7	c.817G>A	p.G273R	Paternal	Reported	VWFA
P2	Compound heterozygous	Exon13	c.1794dupC	p.N599Qfs*93	Paternal	Novel	CYS4
		Exon7	c.850G>A	p.G284S	Maternal	Reported	VWFA
P3	Compound heterozygous	Exon13	c.1788C>A	p.C596X	Paternal	Novel	CYS4
		Exon7	c.817G>A	p.G273R	Maternal	Reported	VWFA
P4	Compound heterozygous	Exon7	c.841-849del9	–	Paternal	Novel	VWFA
		Entire gene	deletion	–	Maternal	Reported	–
P5	Compound heterozygous	Exon6	c.533C>T	p.Pro178Leu	Paternal	Reported	VWFA
		Exon7	c.769C>T	p.Arg257Trp	Maternal	Reported	VWFA
P6	Compound heterozygous	Exon6	c.741+1delG	–	Paternal	Novel	–
		Exon7	c.897+1G>A	–	Maternal	Reported	–
P7	Compound heterozygous	Exon2-Exon8	deletion	–	Paternal	Novel	–
		Exon4	c.322C>T	p.R108X	Maternal	Reported	–

patients who were beyond 1 year old in our study. Thus, patients with severe periodontitis in early life should be transferred to an immunologist. The pathogens including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecium*, and *Candida parapsilosis* have been found in our patients, which are similar to the previously reported cases. Interestingly, CMV infection is very common in our patients. It may be related to the high incidence of CMV infection in our country.

Out of the seven patients, six patients had a delayed cord separation after the second week of life in our study. Elena et al. [9] reviewed 323 cases with LAD-I published before 2017 and concluded that there was a significant correlation between the absence of umbilical cord complications and

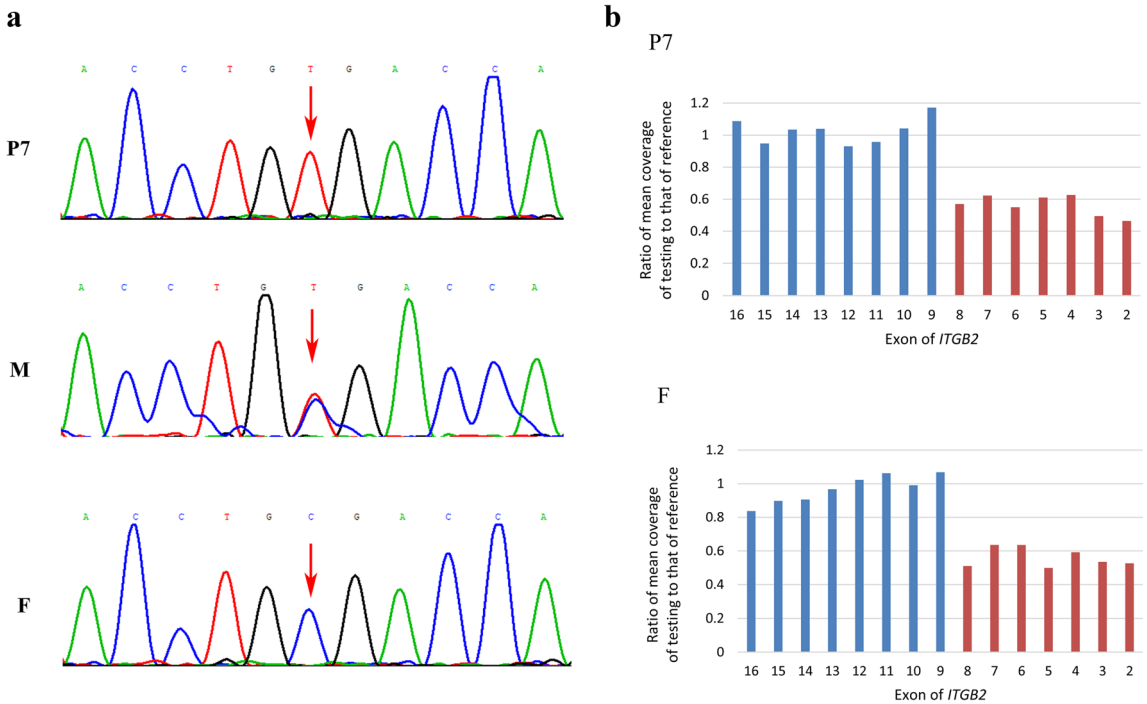

Fig. 2 Gene analysis of *ITGB2* in P7 family. **a** Point mutation (c.322C>T, p.R108X) in P7 family. P7: Patient 7 had a c.322C>T homozygous mutation confirmed by Sanger sequencing. M: mother of P7, who had c.322C>T heterozygous mutation. F: father of P7, who had no c.322C>T mutation. **b** A heterozygous deletion from exon 2 to exon 8 in the *ITGB2* gene were detected by the reduced NGS sequence reads, which derived from her father. These data showed that P7 had one allele with c.322C>T heterozygous mutation derived from her mother and another allele with deletion derived from her father

survival to 24 months for patients with CD18 less than 2%. The delayed cord separation is one symptom of concern to clinicians. Persistent leukocytosis has yet to be another significant feature of LAD-I [22]. It was noted in all our patients and the white blood cell count can be even higher during the infection period. Interestingly, two patients in this study presented with only 11 × 10^9/L white blood cells during infection-free time. These data indicate that we should pay attention to identify the disease, even if the patient has no leukocytosis.

Flow cytometric analysis of CD18 and CD11 (a, b, c) expressions on peripheral blood leukocytes is considered a rapid, sensitive, and hence, commonly used tool for confirmation of diagnosis [23]. According to the expression of CD18, LAD-I can be categorized into two forms: the severe form of the disease (less than 2% expression of CD18) and the moderate form of the disease (between 2 and 30% expression of CD18) [7]. In the current study, all seven patients showed low expression levels of CD18. Two patients showed less than 2% CD18 expression. To make a prenatal diagnosis of LAD-I, the expression of CD18 can be measured by the age of 20 weeks, and assessment of CD18 expression on fetal blood lymphocytes can be used [24]. However, Wolach et al. [25] reported a cohort of 18 LAD-I patients in which six patients had positive CD18 expression and lower CD11a expression. It indicated that we could not rule out the disease according to the normal expression of CD18.

The "suspected LAD-I patients" are not conclusive until genetic information is available. LAD-I is caused by mutations in the *ITGB2* gene, which is autosomal recessive inheritance. A recent update on genetic analysis of LAD-I revealed more than 100 different mutations, of which missense and frameshift mutations were most frequent, moreover, mutations on exons 5, 6, and 7 accounted for 44% [9]. Four Chinese patients were reported previously, including the following mutations [10–13]: c.954del G, c.1802C>A, c.1768T>C, c.899A>T, and c.897+1G>A. In the present cohort, gene analysis was performed in all seven patients, which revealed 13 mutations, including missense (38.5%), nonsense (15.4%), slicing (15.4%), frameshift (15.4%), and gross deletion (15.4%) mutations. Four novel mutations were identified: c.1794dupC, c.1788C>A, c.841-849del9, and c.741+1delG. Six patients had compound heterozygous mutations, whereas the majority of the previously published cases had homozygous mutations. These results may be associated with the lack of consanguine marriages in China. P1 was the only homozygote without deletion, whose father was heterozygous and mother was normal in *ITGB2*. We guess that might be a de novo mutation on the other allele of the patient or his mother had mosaicism in germ cells, which were not genetically tested. In this cohort, we discovered that two patients harbored one large gene deletion (the entire gene or exon 2-exon 8), which has only been previously reported in very few cases [5, 26–28]. Notably, gross deletions might occur in patients, which might be overlooked by the clinicians, leading to misdiagnoses. Further investigations should be carried out when the patient manifests typical LAD-I symptoms but only one mutation is found in the gene.

The disease can be cured by hematopoietic stem cell transplantation (HSCT) [7]. Outcomes for 101 LAD-I patients receiving HSCT were available in previously reported cases. Successful transplantation was reported to be 73.3% (74/101), regardless of the HSCT type, while transplant-related mortality was 19% [9]. In our study, UCBSCT was performed in five patients, and all patients achieved successful phenotypic correction and were in good condition until the last follow-up. In 2017, Moutsopoulos et al. reported that ustekinumab, interleukin-12, and interleukin-23 signaling inhibitor, had a role in the management of LAD-I [29]. It will be the new direction of management of LAD-I.

In conclusion, we reported the clinical manifestations and treatment of seven Chinese patients with LAD-I. In addition, four novel mutations were reported, extending the *ITGB2* gene mutation database. These results are helpful in understanding the current status of the disease in China.

Acknowledgments We thank the patients and their families for their cooperation.

Funding Information This study was supported by the National Natural Science Foundation of China (81471482, 81373221) and the Children's Hospital of Fudan University Funding (EK1125180110, EK112520180202).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Harris ES, Weyrich AS, Zimmerman GA. Lessons from rare maladies: leukocyte adhesion deficiency syndromes. Curr Opin Hematol. 2013;20(1):16–25.
2. Etzioni A. Leukocyte adhesion deficiencies: molecular basis, clinical findings, and therapeutic options. Adv Exp Med Biol. 2007;601:51–60.
3. Movahedi M, Entezari N, Pourpak Z, Mamishi S, Chavoshzadeh Z, Gharagozlou M, et al. Clinical and laboratory findings in Iranian patients with leukocyte adhesion deficiency (study of 15 cases). J Clin Immunol. 2007;27(3):302–7.
4. Hogg N, Stewart MP, Scarth SL, Newton R, Shaw JM, Law SK, et al. A novel leukocyte adhesion deficiency caused by expressed but nonfunctional beta2 integrins Mac-1 and LFA-1. J Clin Invest. 1999;103(1):97–106.
5. van de Vijver E, Maddalena A, Sanal O, Holland SM, Uzel G, Madkaikar M, et al. Hematologically important mutations: leukocyte adhesion deficiency (first update). Blood Cells Mol Dis. 2012;48(1):53–61.
6. Hanna S, Etzioni A. Leukocyte adhesion deficiencies. Ann N Y Acad Sci. 2012;1250:50–5.

7. van de Vijver E, van den Berg TK, Kuijpers TW. Leukocyte adhesion deficiencies. Hematol Oncol Clin North Am. 2013;27(1):101–16.
8. Madkaikar M, Italia K, Gupta M, Chavan S, Mishra A, Rao M, et al. Molecular characterization of leukocyte adhesion deficiency-I in Indian patients: identification of 9 novel mutations. Blood Cells Mol Dis. 2015;54(3):217–23.
9. Almarza NE, Kasbekar S, Thrasher AJ, Kohn DB, Sevilla J, Nguyen T, et al. Leukocyte adhesion deficiency-I: a comprehensive review of all published cases. J Allergy Clin Immunol Pract. 2018;6(4):1418–20.
10. Liu JR, Zhao SY, Jiang ZF. Clinical analysis of a Chinese child with leukocyte adhesion deficiency type 1[J]. Chin J Pediatr. 2013;51(7):531–4.
11. Wang T, Jiang LP, Gao H, Zhao XD. Clinical and molecular features of one case of leukocyte adhesion deficiencytype-1 [J]. Immunol J. 2017;33(8):697–702.
12. Lin Y, Zheng HY, Xian YY, Chang H, Lei K, Wang BT, et al. Novel mutations of ITGB2 induced leukocyte adhesion defect type 1 [J]. Chin J Pediatr. 2018;56(8):617–22.
13. Tsai YC, Lee WI, Huang JL, Hung IJ, Jaing TH, Yao TC, et al. Neutrophil function and molecular analysis in severe leukocyte adhesion deficiency type I without separation delay of the umbilical cord. Pediatr Allergy Immunol. 2008;19(1):25–32.
14. Wang Y, Wang W, Liu L, Hou J, Ying W, Hui X, et al. Report of a Chinese cohort with activated phosphoinositide 3-kinase delta syndrome. J Clin Immunol. 2018;38(8):854–63.
15. Wang J, Yu H, Zhang VW, Tian X, Feng Y, Wang G, et al. Capture-based high-coverage NGS: a powerful tool to uncover a wide spectrum of mutation types. Genet Med. 2016;18(5):513–21.
16. Hayward AR, Harvey BA, Leonard J, Greenwood MC, Wood CB, Soothill JF. Delayed separation of the umbilical cord, widespread infections, and defective neutrophil mobility. Lancet. 1979;1(8126):1099–101.
17. Springer TA, Thompson WS, Miller LJ, Schmalstieg FC, Anderson DC. Inherited deficiency of the Mac-1, LFA-1, p150, 95 glycoprotein family and its molecular basis. J Exp Med. 1984;160(6):1901–18.
18. Tewari N, Mathur VP, Yadav VS, Chaudhari P. Leukocyte adhesion defect-I: rare primary immune deficiency. Spec Care Dentist. 2017;37(6):309–13.
19. Etzioni A. Genetic etiologies of leukocyte adhesion defects. Curr Opin Immunol. 2009;21(5):481–6.
20. Cox DP, Weathers DR. Leukocyte adhesion deficiency type 1: an important consideration in the clinical differential diagnosis of prepubertal periodontitis. A case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105(1):86–90.
21. Majorana A, Notarangelo LD, Savoldi E, Gastaldi G, Lozada-Nur F. Leukocyte adhesion deficiency in a child with severe oral involvement. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;87(6):691–4.
22. Teimourian S, De Boer M, Roos D, Isaian A, Bemanian MH, Lashkary S, et al. Genetic analysis of 13 Iranian families with leukocyte adhesion deficiency type 1. J Pediatr Hematol Oncol. 2018.
23. Deshpande P, Kathirvel K, Alex AA, Korula A, George B, Shaji RV, et al. Leukocyte adhesion deficiency-I: clinical and molecular characterization in an Indian population. Indian J Pediatr. 2016;83(8):799–804.
24. Madkaikar MR, Gupta M, Rao M, Ghosh K. Prenatal diagnosis of LAD-I on cord blood by flowcytometry. Indian J Pediatr. 2012;79(12):1605–9.
25. Wolach B, Gavrieli R, Wolach O, Stauber T, Abuzaitoun O, Kuperman A, et al. Leucocyte adhesion deficiency-a multicentre national experience. Eur J Clin Investig. 2019;49(2):e13047.
26. Bernard CT, Chan HS, Klein GF, Jabkowski J, Schadenbock-Kranzl G, Zach O, et al. A novel 3' splice-site mutation and a novel gross deletion in leukocyte adhesion deficiency (LAD)-1. Biochem Biophys Res Commun. 2011;404(4):1099–104.
27. Fiorini M, Piovani G, Schumacher RF, Magri C, Bertini V, Mazzolari E, et al. ITGB2 mutation combined with deleted ring 21 chromosome in a child with leukocyte adhesion deficiency. J Allergy Clin Immunol. 2009;124(6):1356–8.
28. Roos D, Meischl C, de Boer M, Simsek S, Weening RS, Sanal O, et al. Genetic analysis of patients with leukocyte adhesion deficiency: genomic sequencing reveals otherwise undetectable mutations. Exp Hematol. 2002;30(3):252–61.
29. Moutsopoulos NM, Zerbe CS, Wild T, Dutzan N, Brenchley L, DiPasquale G, et al. Interleukin-12 and Interleukin-23 blockade in leukocyte adhesion deficiency type 1. N Engl J Med. 2017;376(12):1141–6.