CORRESPONDENCE

A Novel Mutation of Ribosomal Protein S19 Gene in a Chinese Child with Diamond-Blackfan Anemia

Hua Jiang¹ · Man-Yu Wu² · Dong-Zhi Li²

Received: 17 January 2015 / Accepted: 3 March 2015 / Published online: 13 March 2015
© Indian Society of Haematology & Transfusion Medicine 2015

Diamond-Blackfan anemia (DBA; OMIM 205900) is a rare congenital erythroid aplasia that usually presents in infancy [1]. The anemia is discovered early in life, usually within the first 2 years; diagnosis after 4 years of age is very unlikely. Physical anomalies are present in up to 50 % of patients with a wide range of severity. Patients have a modest increased risk of developing leukemia and other malignancies. DBA moved into the scientific limelight after the unexpected identification of the first DBA gene, ribosomal protein S19 (RPS19) [2]. The finding of mutations affecting other ribosomal protein genes establishes DBA as a disorder of ribosomal biogenesis and/or function. Here, we report the first Chinese DBA patient with a novel mutation in RPS19.

A 12-year-old boy was referred to our hospital with anemia with no other significant cytopenias. His parents and an 8-year-old sister were healthy. Pallor was first found at 1 month after birth and the patient had received two blood transfusions within the first 2 months of life. The diagnosis of DBA was established by 3 months by bone marrow aspiration which showed normocellular marrow with myeloid-to-erythroid ratio of 60:1, grossly reduced red cell precursors and normal other cell lines. The patient was then treated with glucocorticoid. He had a good response to steroids until 7 years old; during the treatment

period his hemoglobin levels maintained 11–12 g/dL. Since then, he failed to respond to steroids. Chronic transfusion therapy with iron chelation was reinstituted. He received transfusion every 2–3 weeks to maintain a hemoglobin level between 8 and 9 g/dL.

At this referral, the patient's height was 151 cm and weight 51.5 kg. His mental status was normal. He had no congenital malformations and no other cytopenias. A repeat marrow biopsy was not done. Genetic studies were performed for screening the mutations in the eight genes known to be associated with DBA, RPS19, RPS24, RPS17, RPL5, RPL11, RPL35A, RPS10, and RPS26. A missense point mutation (c.188A > C; p.His63Pro) was identified in the exon 4 of RPS19 gene in the patient (Fig. 1). However, this mutation was not found in either of the parents (Fig. 1), thus suggesting a *de novo* origin. The c.188A > C variant of RPS19 has not been reported previously following literature search in PubMed and mutation search in web-accessible Leiden Open Variation Database (LOVD). To confirm that c.188A > C in the RPS19 gene is not a polymorphism, a total of 100 unrelated healthy individuals were also screened for the same mutation. This mutation was not identified in 200 control chromosomes.

DBA has been associated with heterozygous mutations in ten ribosomal protein (RP) genes; six small subunit RP genes RPS7, RPS10, RPS17, RPS19, RPS24, and RPS26; and four large subunit RP genes RPL5, RPL11, RPL35A, and RPL26 [3, 4]. Mutations in these genes have been reported in ~55 % of DBA patients. The RPS19 protein plays an important role in 18S rRNA maturation in both yeast and human cells [5, 6]. All the RPS19 mutations were found in heterozygosity with the wild-type sequence; this is consistent with the dominant inheritance pattern and with the evidence that the RPS19 knockout is lethal prior to

✉ Dong-Zhi Li
drlidongzhi2014@sina.com

¹ Department of Hematology/Oncology, Guangzhou Women & Children Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China

² Prenatal Diagnostic Center, Guangzhou Women & Children Medical Center, Guangzhou Medical University, Jinsui Road 9, Zhujiang New Town, Guangzhou 510623, Guangdong, China

Fig. 1 Direct sequencing showed a c.188A > C mutation at the exon 4 of RPS19 gene. **a** Mutant allele; **b** wild allele

implantation in mice [7]. Mutations are heterogeneous and span the whole gene, and missense mutation is the most frequent subtype. According to its location on protein structure, the p.His63Pro belongs to class II mutations. These mutations, which are much more conserved, are located on the surface of RPS19 and hence may affect its interaction with its environment and impair its function without altering its folding [8].

More than half a century after the original report of their efficacy, steroids remain the mainstay of therapy for patients with DBA. However, the patients may become unresponsive without any known reasons even they have being highly steroid responsive for a long time, as evidenced by our patient. The identification of pathogenic mutations in RPS19 provided a definite diagnosis of DBA in this patient who was waiting for a suitable donor for hemopoietic stem cell transplantation.

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

Ethical Statement The authors declare that they have no competing interests. The work was carried out according to the principles of the Declaration of Helsinki and approved by the ethics committee of Guangzhou Women & Children Medical Center. Informed consent was obtained from the parents.

References

1. Vlachos A, Blanc L, Lipton JM (2014) Diamond Blackfan anemia: a model for the translational approach to understanding human disease. *Expert Rev Hematol* 7:359–372
2. Draptchinskaia N, Gustavsson P, Andersson B et al (1999) The gene encoding ribosomal protein S19 is mutated in Diamond-Blackfan anemia. *Nat Genet* 21:169–175
3. Delaporta P, Sofocleous C, Stiakaki E et al (2014) Clinical phenotype and genetic analysis of RPS19, RPL5, and RPL11 genes in Greek patients with Diamond Blackfan Anemia. *Pediatr Blood Cancer* 61:2249–2255
4. Landowski M, O'Donohue MF, Buros C et al (2013) Novel deletion of RPL15 identified by array-comparative genomic hybridization in Diamond-Blackfan anemia. *Hum Genet* 132:1265–1274
5. Flygare J, Aspesi A, Bailey JC et al (2007) Human RPS19, the gene mutated in Diamond-Blackfan anemia, encodes a ribosomal protein required for the maturation of 40S ribosomal subunits. *Blood* 109:980–986
6. Léger-Silvestre I, Milkereit P, Ferreira-Cerca S et al (2004) The ribosomal protein Rps15p is required for nuclear exit of the 40S subunit precursors in yeast. *EMBO J* 23:2336–2347
7. Matsson H, Davey EJ, Draptchinskaia N et al (2004) Targeted disruption of the ribosomal protein S19 gene is lethal prior to implantation. *Mol Cell Biol* 24:4032–4037
8. Gregory LA, Aguisa-Toure AH, Pinaud N, Legrand P, Gleizes PE, Fribourg S (2007) Molecular basis of Diamond-Blackfan anemia: structure and function analysis of RPS19. *Nucleic Acids Res* 35:5913–5921