

Case Report  
Laboratory Medicine



# The First Case of Para-Bombay Blood Type Encountered in a Korean Tertiary Hospital

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OPEN ACCESS

Received: Jun 16, 2019

Accepted: Aug 19, 2019

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## ABSTRACT

Para-Bombay phenotypes are rare blood groups that have inherent defects in producing H antigens associated with *FUT1* and/or *FUT2*. We report the first case of para-Bombay blood type in a Southeast Asian patient admitted at a tertiary hospital in Korea. A 23-year-old Indonesian man presented to the hospital with fever and was diagnosed with a disseminated nontuberculous mycobacterium infection and anemia. During blood group typing for blood transfusion, cell typing showed no agglutination with both anti-A and anti-B reagents. Serum typing showed strong reactivity against B cells and trace agglutination pattern with A1 cells. His red blood cells failed to react with anti-H reagents. Direct sequencing of *FUT1* and *FUT2* revealed a missense variation, c.328G>A (p.Ala110Thr, rs56342683, *FUT1*\*01W.02), and a synonymous variant, c.390C>T (p.Asn130=, rs281377, *Se*<sup>357</sup>), respectively. This highlights the need for both forward and reverse grouping.

**Keywords:** Human *FUT1* Protein; Human *FUT2* Protein; H Blood Group System

## INTRODUCTION

Bombay and para-Bombay phenotypes are rare blood groups that have inherent defects in producing H antigens. The molecular basis of these rare blood types has been proven to be mutations of the *FUT1* (H gene) or *FUT2* (Se gene).<sup>1-4</sup> The para-Bombay type is different from the Bombay type in that the former has H antigens in secretions, whereas the latter does not.<sup>1</sup>

The first report of this rare blood type was from India in 1952.<sup>5</sup> Following this, there have been several reports regarding these rare blood groups; to the best of our knowledge, none have been reported from Korea.<sup>6-10</sup> Herein, we report the case of a Southeast Asian patient admitted at a tertiary hospital in Korea with a para-Bombay phenotype.

**Disclosure**

The author has no potential conflicts of interest to disclose.

**Author Contributions**

Conceptualization: Oh HB, Ko DH. Data curation: Kim MS, Ko DH. Formal analysis: Kim MS. Methodology: Kim MS, Kim JS. Software: Park H, Chung Y, Kim SH. Writing - original draft: Kim MS, Ko DH. Writing - review & editing: Kim MS, Ko DH. Oh HB, Kim H, Hwang SH.

**CASE DESCRIPTION**

In December of 2018, a 23-year-old Indonesian man presented to Asan Medical Center with a 2-week history of fever, chills, and headache. He entered Korea 2 years previously. He had never received a blood transfusion. Initial blood tests revealed anemia and thrombocytosis. The initial laboratory test results were as follows: white blood cells,  $14.8 \times 10^9/L$ ; hemoglobin, 8.2 g/dL (82 g/L); platelets,  $624.0 \times 10^9/L$ ; mean corpuscular volume, 79.0 fL; mean corpuscular hemoglobin, 24.8 pg; mean corpuscular hemoglobin concentration, 31.4%; iron, 16  $\mu\text{g/dL}$  (160  $\mu\text{g/L}$ ); total iron binding capacity, 156  $\mu\text{g/dL}$  (1,560  $\mu\text{g/L}$ ) and ferritin, 1,267.9 ng/mL. Nontuberculous mycobacteria (NTM) isolates were identified in an axillary lymph node biopsy specimen using the nested MTB & NTM Kit (BioSewoom Inc., Seoul, Korea). He was diagnosed with disseminated NTM infection and was then treated accordingly.

The patient subsequently developed anemia of chronic disease combined with iron deficiency anemia and therefore a blood transfusion was recommended due to severe microcytic anemia. Blood typing was performed using IH-1000 (Bio-Rad Laboratories Inc, Hercules, CA, USA). His RBCs showed no reactivity against both anti-A and anti-B serum, while his serum showed agglutination with only B cells. The result of the pretransfusion RBC antibody screening test (ID-DiaCell I-II, BIO-RAD; Hercules) was negative.

Manual tube testing was then performed to resolve the discrepancy. Forward grouping showed no agglutination with monoclonal anti-A and anti-B serum (SIHDIA Anti-A and Anti-B; Shinyang diagnostics, Seoul, Korea). Reverse grouping using A1 and B cells (iMR. A1-B; MIRR. SciTech Corp., Seoul, Korea) showed trace and 4+ agglutinations with group A1 and group B cells, respectively. When we incubated the serum with RBCs for an extra 15–30 minutes, the results did not change. After cold adsorption and elution of RBCs with anti-A, the eluate showed trace agglutination with A1 cells. H antigen tests using two different antiserum (Lorne laboratories, Danehill, United Kingdom; ANTITOXIN GmbH, Bammental, Germany) revealed that the patient's RBCs did not express H antigens (Table 1). Crossmatching with 10 units of O type RBCs showed consistently incompatible results with a grade  $\pm \sim 2+$  agglutination of O type RBCs in the saline phase and 22% in the bovine albumin and antiglobulin phase.

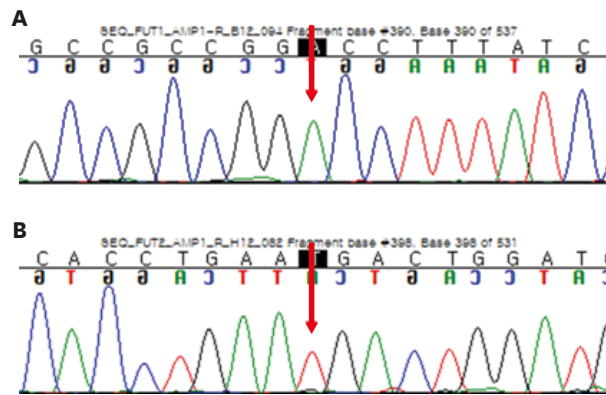
ABO genotyping using sequencing for exon 6, exon 7 and their flanking regions revealed that the patient had an A/O allele combination. Direct sequencing analysis for coding regions and their flanking areas of *FUT1* and *FUT2* were performed.<sup>9</sup> We found one missense variation, NM\_000148.3:c.328G>A (p.Ala110Thr, rs56342683, *FUT1*\*01W.02), as a homozygote in *FUT1*. A synonymous variant, NM\_000511.5:c.390C>T (p.Asn130=, rs281377, *Se*<sup>357</sup>), was found in *FUT2*, also in the homozygous state (Fig. 1). Based on these results, the patient's blood group was confirmed to be para-Bombay type.

**Table 1.** Results of ABO blood group typing

Variables	Forward typing				Reverse typing			
	Anti-A	Anti-B	Anti-A1	Anti-H	A1 cells	B cells	O cells	Auto
Column agglutination	-	-	NT	NT	-	4+	NT	NT
Tube testing (RT)	-	-	-	-	$\pm$	4+	-	-
Elute testing <sup>a</sup>	NA	NA	NA	NA	$\pm$	NA	NA	NA

NT = not tested, RT = room temperature, NA = not applicable, - = negative, + = positive,  $\pm$  = trace.

<sup>a</sup>Cold adsorption of red cells with anti-A and elution at 56°C.

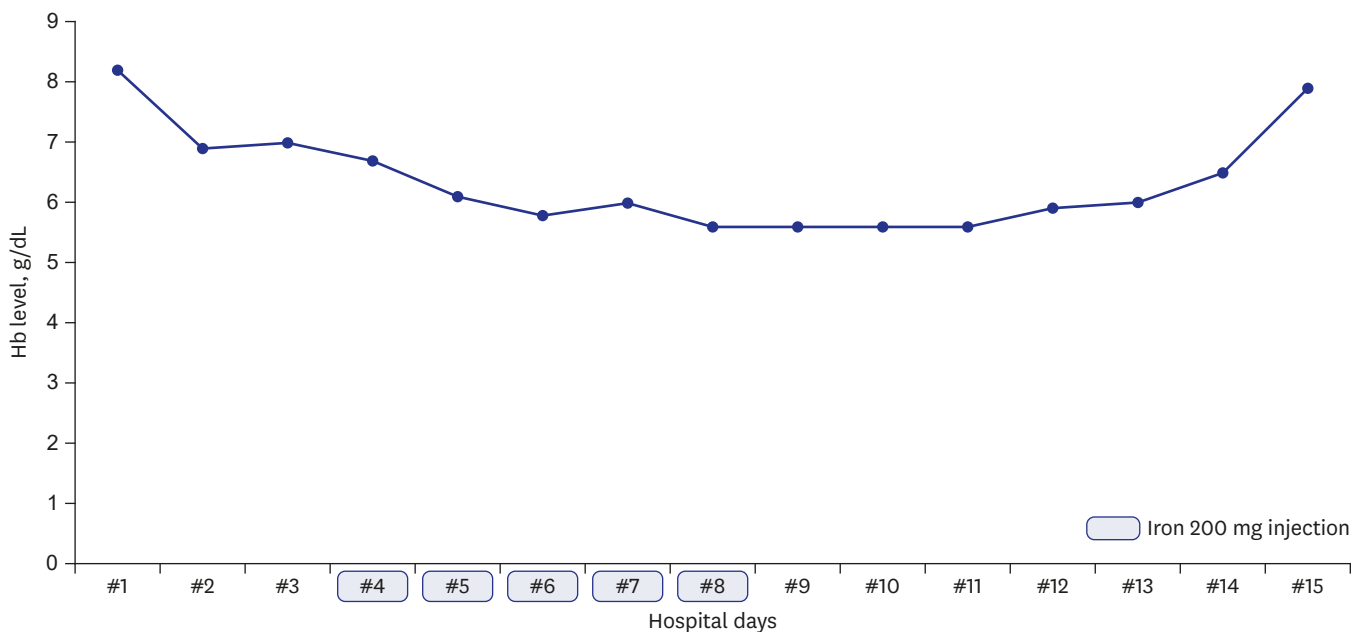


**Fig. 1.** Sequencing chromatograms of analyzed genes. (A) Result for *FUT1* and (B) result for *FUT2*. The arrows indicate the variants in *FUT1* (c.328G>A, p.Ala110Thr) and *FUT2* (c.390C>T, p.Asn130=). Each variant represents *FUT1*<sup>O1W.O2</sup> and *Se*<sup>357</sup> allele, respectively.

Because compatible blood could not be found and familial donors were unavailable, he was administered intravenous iron sucrose (Venoferrum; Vifor International, Ltd., St Gallen, Switzerland) for five consecutive days for treating anemia. After 15 days of admission, the hemoglobin level increased to 7.9 g/dL, and his clinical symptoms were relieved. He was discharged without receiving the RBC transfusion (Fig. 2).

**Ethics statement**

All experiments were conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Reporting of this case without informed consent was approved by the Institutional Review Board of Asan Medical Center (AMC 2018-0435).



**Fig. 2.** Changes in Hb levels. Hb level decreased to 5.6 g/dL from the initial value of 8.2 g/dL. Hb level then increased to 7.9 g/dL after a total of 1,000 mg of intravenous iron sucrose. Hb = hemoglobin.

## DISCUSSION

Molecular mechanisms underlying Bombay and para-Bombay blood groups were identified several decades ago.<sup>11</sup> Individuals with para-Bombay type may have weak A or B antigens depending on their ABO alleles.<sup>12</sup> In this case, the patient's phenotype was determined as Ah, i.e., weak A expression revealed by adsorption-elution.

The Bombay blood group is mostly confined to South East Asian countries. Approximately 1/1,000 individuals in India have a "Bombay blood group." In Caucasians, the incidence was found to be 1/250,000.<sup>13</sup> The para-Bombay phenotype may be less frequent than the Bombay phenotype, particularly in Japan, where the incidence of Bombay and para-Bombay phenotypes were shown to be 1–2 in 300,000.<sup>14</sup> In Taiwan, the incidence of the para-Bombay phenotype was estimated to be 1 in 8,000 residents based on the serological analysis.<sup>15</sup>

Bombay and para-Bombay phenotypes arise from the inheritance of two non-functional *FUT1* alleles (usually designated as hh). Two entities are distinguished by the presence or absence of *FUT2*, known as a secretory gene. The H antigens are deficient on RBCs, but they are present in secretions from para-Bombay individuals (hh, Se/Se or Se/se).<sup>12</sup> These can be absorbed into RBCs which then demonstrate weak A (Ah) or B (Bh) expressions.

In this case, *FUT1* gene sequence analysis revealed that the patient harbored a homozygous variation, c.328G>A (p.Ala110Thr, rs56342683, *FUT1*\*OIW.02). Although this variant has been classified as a weak H allele according to the International Society of Blood Transfusion classification, a Chinese study reported that this allele was found in para-Bombay phenotype.<sup>16,17</sup> *FUT2* gene sequence analysis revealed a synonymous variant *Se*<sup>357</sup> that has been reported as a major secretor allele in various races.<sup>18,19</sup> From the results of these studies and the patient's phenotype, we could conclude that the patient has a para-Bombay blood type. These mutations pose huge challenges when performing transfusions on patients. Thus, laboratory staff should be aware of these variations.

Naturally occurring anti-H is of clinical relevance to individuals with Bombay and para-Bombay blood types. These patients should be transfused with only Bombay or para-Bombay blood due to the presence of preformed antibodies in their serum, which makes it impossible to find compatible blood in institutions' blood banks. As para-Bombay blood type has been reported several times in Asia, especially in China, it is highly likely that this rare blood type is also found in Korea.<sup>9,19</sup> This highlights the urgency and importance of establishing frozen blood banks for rare blood groups.

At the first instance, the patient was interpreted to have O blood group. The suspicion of a rare variant arose from the results of reverse typing. This re-emphasizes the importance of the concurrent use of forward and reverse grouping techniques for blood group determination. Rare blood groups such as Bombay and para-Bombay cannot be determined without using anti-H reagents; in the absence of anti-H antigens, such individuals are misidentified as having blood group O, and this could lead to fatal transfusion reactions. Unfortunately, some clinical laboratories in Korea are still not equipped with anti-H reagents. The use of anti-H reagents should be expanded in Korea.

Although the hemoglobin levels decreased to 5.6 g/dL, iron supplementation alone increased the hemoglobin levels to 7.9 g/dL. This exemplifies that unnecessary transfusions

could be avoided with appropriate medication. This management also illustrated the possibility of managing blood inventories.

Although there have been no formal reports regarding Bombay and para-Bombay blood types in Korea, several cases have been published from Southeast Asia and China.<sup>7,9</sup> As the ethnic diversity in Korea is expanding, laboratory staff and clinicians in Korea should be aware of this rare blood group and be prepared to manage patients appropriately.

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