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Further observation of Hemoglobin Fontainebleau (a21(B2) Ala-Pro) in a Turkish family

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To the Editor,

Several hemoglobin (Hb) variants have been reported in Turkish population [1–3]. Herein, we represent a nucleotide alteration of the alpha-2 chain variant, Hemoglobin Fontainebleau (a21(B2) Ala-Pro) in an 8-year-old male Turkish child living in Ankara, Turkey. He was admitted to the Hospital Pediatrics Department for routine check-up. His physical examination was normal, and there was no positive consanguinity between his parents. High red blood cell count and low mean corpuscular volume were detected in complete blood count (CBC) (Fig. 1a). High-performance liquid chromatography (HPLC) showed an asymmetry (shoulder formation) in the descending part of A0 and in the A2 curve. Levels of HbA, HbA2, and HbF were observed as 93.25%, 3.55%, and 1.07%, respectively (Fig. 1a). His mother and 6-year-old sister were also screened. Their HPLC chromatograms showed similar pattern (Fig. 1b, c).

Sequence analysis of HBA1 and HBA2 genes were performed by using MiSeq next-generation sequencing (NGS) platform (Illumina, San Diego, CA, USA). Genomic DNA was extracted by using the QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany). All coding regions and exon-intron boundaries of the genes were amplified using PCR primers, designed with PRIMER©-Primer Designer v.2.0 (Scientific & Educational Software programme) software. Alignment was done by using hg19 genome with MiSeq Reporter software (Illumina Inc.), and analysis was done with IGV 2.3 (Broad Institute) software. These genes were also tested for common deletions with MLPA (multiplex ligation-dependent probe amplification) method (SALSA MLPA P140 HBA probemix, MRC Holland, Amsterdam, Holland). NM_000558.5(HBA1):c.64G>C (p.Ala22Pro) was detected by sequence analysis while MLPA test was normal (Fig. 1a, b).

Written informed consent for genetic analysis was obtained both from the child's parents and from the mother.

Hemoglobin Fontainebleau (a21(B2) Ala-Pro) is a rarely reported hemoglobin variant. It was first reported in an Italian family without DNA analysis in 1989 and later on in India, Canada, South Cyprus, United Arab Emirates, Iraq (family living in New Zealand), and Turkey. It was described as a silent mutation and was also reported in combination with heterozygote forms of sickle cell, hereditary spherocytosis, and Hb Punjab [1, 4–6].

It is interesting that the cases identified were on historical migration routes. Since Turkey is located at the intersection of two continents, it is not surprising that many different hemoglobin variants are observed. Further observation of Hb Fontainebleau (a21(B2) Ala-Pro) suggests that this variant is found sporadically in the Turkish population.

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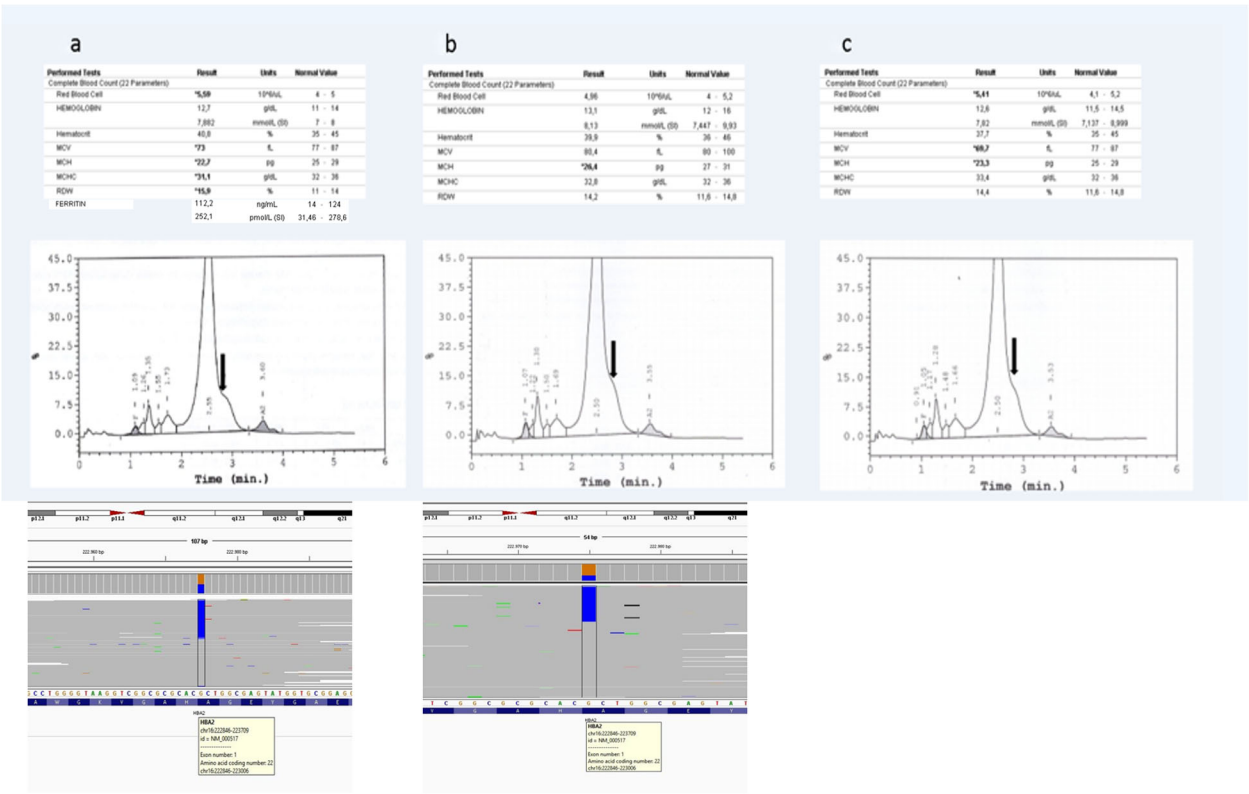

Fig. 1 CBC, HPLC chromatograms, and HBA2 gene. The figure includes the HPLC histograms and HBA2 gene sequence analysis below the complete blood count and ferritin levels of the patient (**a**), his mother (**b**), and sister (**c**). The asymmetry (shoulder formation) in the descending part of A0 and in the A2 curve was indicated with an arrow on the chromatogram

Abbreviations
CBC: Complete blood count; Hb: Hemoglobin; HPLC: High-performance liquid chromatography; MLPA: Multiplex ligation-dependent probe amplification; NGS: Next-generation sequencing

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NA contributed to the clinical diagnosis and reviewing of the manuscript. SC contributed to the sequence analysis. YAA contributed to the drafting and reviewing of the manuscript. GST contributed to the drafting of the manuscript. All authors have read and approved the final manuscript.

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Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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