The First Case of Hemoglobin Beckman Beta135(H13) ALA>ASP Identified in Turkey

Türkiye’de Tanınlanan İlk Hemoglobin Beckman Beta135(H13) ALA>ASP Olgusu

As a Mediterranean country, the frequency of thalassemias and hemoglobinopathies is fairly high in Turkey. This article describes the first case of Hemoglobin Beckman in Turkey. This variant was observed in a 56-year-old Caucasian man during the HbA1c measurement with a cation exchange high performance liquid chromatography (CE-HPLC). Gene sequencing analysis revealed an heterozygote codon 135 GCT-GAT (Ala --> Asp) mutation which was identical for the Hemoglobin Beckman in the Globin Gene Server (HGVS: HBB:c.407C>A). The case was similar, in terms of DNA sequence result and clinical signs to the Hemoglobin Beckman case reported by Kim et al. in 2010, rather than the first case described for the first time by Rahbar et al. in 1991.

Key Words: Hemoglobinopathies; hemoglobins, abnormal


Anahtar Kelimeler: Hemoglobinopatiler; hemoglobinin, anormal

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The most common inherited diseases in humans result from mutations in the beta and alpha globin gene complex. Single nucleotide substitutions can lead to amino acid replacements that cause hemolytic anemias, such as sickle-cell disease, or hemoglobin variants that are unstable or have altered oxygen affinity. Substitutions or deletions, which occur in any of several regions of the genes cause the inherited anemia called thalassemia. Some other sequence changes have little or no effect on hemoglobin function, but are useful polymorphisms for genetic studies. More than 1000 hemoglobin variants have been identified to date and new variants and thalassemias continue to be discovered.1

Abnormal hemoglobins are the second most common hemoglobinopathies after beta thalassemia in the Turkish population. To date, more
than 40 different hemoglobin variants have been reported in the Turkish population. Some of these abnormal hemoglobins were originally described in the Turkish population.

**CASE REPORT**

A 56 year old Caucasian man with controlled diabetes mellitus presented to the biochemistry laboratory of Dr. Lütfi Kirdar Kartal Training and Research Hospital for the determination of HbA1c. The HbA1c value could not be determined by the cation exchange high performance chromatographic (CE-HPLC) (Variant II Turbo, Biorad) method used in the laboratory and an unusual peak was observed on the chromatogram.

Thereon, the samples of the propositus and the family members (mother, daughter and niece) were investigated for their hematological status and the presence of any hemoglobin variant. An informed consent was signed by the patient and the family members.

The hematological parameters were measured by the routine blood count analyser (Sysmex XT 2000i, Roche Diagnostic). The hematological results of the propositus and the mentioned family members are shown in the table (Table 1). The hematological values of the propositus and his daughter and niece were within the reference ranges; however the mother’s values indicated an anemia which was consequently diagnosed as iron deficiency anemia.

The sample of the propositus and family members were then evaluated for the presence of a variant by two CE-HPLC methods (Variant II Turbo, Biorad and Ultra2-Variant, Trinity-Biotech); on the chromatogram of the propositus with the first system, there was a peak eluting at LHbA1c/CHb-1 fraction with an area of 49.1% (Figure not shown). The variant generated a peak with an area of 46.7% eluting after HbA1c with the second system (Figure 1). The chromatograms of tree members of the family showed the same peak with similar percentages.

DNA isolation from blood samples collected in EDTA tubes was carried out using a commercially available DNA extraction kit (RTA Lab, Ltd., Sti, Türkiye). Beta globin gene regions were sequenced with an ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, CA., USA), according to the manufacturer’s instructions; and finally, ABI PRISM 310 genetic analyzer (Applied Biosystems, Foster City, California, USA) was utilized to analyze sequence reaction. This beta globin gene sequence analysis revealed an heterozygote codon 135 GCT-GAT (Ala -> Asp) mutation which was identical to the Hemoglobin Beckman (HGVS: HBB:c.407C>A). (Figure 2).

**DISCUSSION**

As mentioned above, disorders resulting structurally abnormal hemoglobins and decreased capacity of globin chain syntesis (thalassemia) are the most common genetic hematological problems; as a Mediterranean country, the frequency of thalassemias and hemoglobinopathies is fairly high in Turkey and more than 40 variants have been reported so far. The majority of the abnormal hemoglobins do not show any clinical signs and are discovered during the investigation of another health problem. In the Globin Gene Server, Hb
Beckman is referred to the case of Rahbar et al. in 1991, described in an 32-year-old African-American female presenting with chronic anemia, microcytosis and splenomegaly. In 2010 Kim et al. reported the second case of Hb Beckman in a 61-year old Korean man with no clinical signs.8 Our patient and his fam-
ily are the first individuals with Hb Beckman detected in Turkey. They were all heterozygotes and otherwise healthy.

These two previous cases were inconsistent in terms of clinical status and DNA sequencing analysis. The case of Rahbar et al. presented with microcytic anemia while the other case was clinically silent. The amino acid sequences of two cases were also discrepant. The first experimental case of Rahbar et al. was described p.Ala136Glu; Hb Beckman alpha2 beta2 135(H13) ala-to-glu. In the Globin Gene Server the Hb Beckman variant was reported as beta 135(H13) Ala —> Asp with a comment noting that an Ala —> Glu change would require a GCA or GCG mutation to GAA or GAG and that the codons GCA and GCG do not occur in the beta-globin gene; GCA is in the gamma gene and GCG in the alpha gene. Landin et al. included Hb Beckman in the group of variants whose reported amino acid substitutions are not compatible with single point nucleotide substitutions. Additionally, this data in the Globin Gene Server was a result of computed information drawn from Rahbar’s case, rather than a direct experimental evidence. Under the circumstances, the case of Kim et al. should be the first single point nucleotide substitution, experimentally confirmed by direct sequencing of Hb variant of p.Ala136Asp.

Our case which is an heterozygote, codon 135 GCT-GAT (Ala —> Asp) mutation seems sequentially and clinically identical to the case of Kim et al. and is seen for the first time in Turkey. We expect that this new case would contribute to elucidate the controversy on the definition of Hb Beckman.

REFERENCES