Keywords: Cholangitis, Döhle bodies, May-Hegglin anomaly

Anahtar Sözcükler: Döhle cisimciği, Kolanjit, May-Hegglin anomalisi

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Address for Correspondence/Yazışma Adresi: Gökhan Özgür, M.D.,
Gülhane Training and Research Hospital, Department of Hematology, Ankara, Turkey
Phone : +90 312 304 4107
E-mail : gokhanozgur2010@hotmail.com **ORCID-ID:** orcid.org/0000-0003-0357-0503

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Three Novel Calreticulin Mutations in Two Turkish Patients

İki Türk Hastada Üç Yeni Kalretikulin Mutasyonu

Veysel Sabri Hançer[1], Hüseyin Tokgöz[2], Serkan Güvenç[3], Ümran Çalışkan[4], Murat Büyükdoğan[1]

[1]İstinye University Faculty of Medicine, Department of Medical Genetics, İstanbul, Turkey
[2]Selçuk University Meram Faculty of Medicine, Department of Pediatric Hematology, Konya, Turkey
[3]Batman District State Hospital, Clinic of Hematology Batman, Turkey
[4]Necmettin Erbakan University Meram Faculty of Medicine, Department of Pediatrics, Konya, Turkey

To the Editor,

Calreticulin (*CALR*) mutations were first identified exclusively in JAK2-MPL-negative essential thrombocythemia (ET) and primary myelofibrosis (PMF) at a rate of 60%-88%, accounting for 1/4 to 1/3 of all patients with ET and PMF [1,2,3]. As of today, more than 55 different types of mutations have been reported. The two most common mutations accounting for 85% of mutated cases are either a 52-bp deletion (type 1; c.1099_1150del; L367fs*46; 44%-53% of cases) or a 5-bp insertion (type 2; c.1154_1155insTTGTC; K385fs*47; 32%-42% of cases). The remaining 15% include various other infrequent mutations that are often unique or found in only a few patients [4,5].

Here we present three *CALR* mutations in two patients with PMF and ET that have not been reported before as shown in Figure 1. Known *CALR* mutations and BCR-ABL, JAK-2 V617F, and MPL 515L/K test results were found to be negative.

Patient 1: The patient was a 46-year-old man with low back pain. Magnetic resonance imaging scanning of the lumbosacral region revealed sacroiliitis on the left side and he was referred to a rheumatologist for further investigations. Anemia (Hb: 10.8 g/dL) and thrombocytosis (700x10^9/L) with a high lactate dehydrogenase level (351 U/L) were found in initial tests. The other tests for a possible rheumatologic disease, including

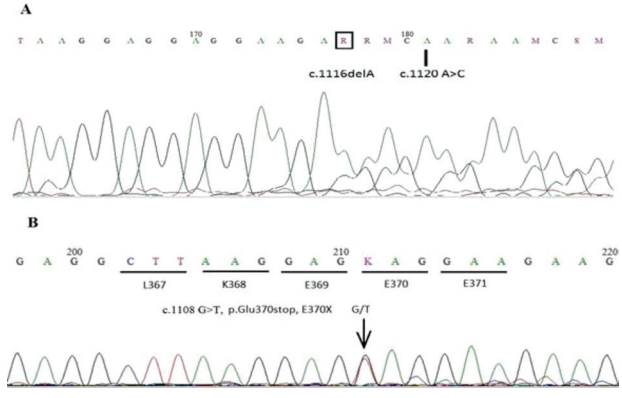

Figure 1. A) Electropherogram result of the primary myelofibrosis patient, B) electropherogram result of the essential thrombocythemia patient.

human leukocyte antigen-B27, were all negative when the patient was seen. Physical examination was almost normal with no sign of organomegaly. Spleen size was also normal in the abdominal ultrasound. The peripheral blood smear showed dacrocytes, occasional myelocytes (1%), and metamyelocytes (1%). The bone marrow biopsy showed diffuse grade 3-4 reticulin fibrosis with atypical proliferation of megakaryocytes and increased cellularity consistent with PMF.

Patient 2: A 9-year-old pediatric patient with thrombocytosis (2800x10^9/L) was identified in a routine check-up. Physical

examination was normal except for mild splenomegaly. Complete blood count revealed increased platelet count ($2800x10^9$/L) with normal hemoglobin and leukocyte count. Platelets were very abundant and clustered in the peripheral blood smear. Bone marrow aspiration and biopsy examinations showed tri-lineage hematopoiesis with an increased number and clusters of megakaryocytes without fibrosis, which is consistent with ET. She had persistently elevated platelet counts ranging between $2000x10^9$/L and $2800x10^9$/L without any evidence of reactive/secondary thrombocytosis such as infections, medicine, autoimmune disorders, neoplasms, trauma, surgery, or hematological disorders such as iron deficient anemia, chronic hemolytic situations, and acute hemorrhages.

Genomic DNA was extracted from whole blood, exon 9 of the *CALR* gene was amplified by polymerase chain reaction, and then the amplified fragments were sequenced. All nucleotide numbers refer to the wild-type cDNA sequence of *CALR* (NM_004343) as reported in Ensembl. Here we report three new *CALR* mutations [1-bp deletion; c.1116delA (D373fs*57) and c.1120 A>C] in the same patient with PMF and c.1108 G>T in a patient with ET. We performed germline testing from the cheek epithelium and both patient samples were confirmed as wild-type *CALR*. These novel mutations occurred and changed the amino acid sequence of the C domain amino acid residues, which will interfere with the calcium-binding capacity of the molecule. It is important to determine the type of mutation. Type 2-like *CALR* mutations are mainly associated with an ET phenotype, low risk of thrombosis, and indolent clinical course, while type 1-like mutations are mainly associated with a myelofibrosis phenotype and a high risk of progression from ET to myelofibrosis. The identification of new *CALR* mutations will improve our understanding of the pathophysiology of myeloproliferative neoplasms.

Keywords: Essential thrombocythemia, Primary myelofibrosis, Calreticulin

Anahtar Sözcükler: Esansiyel trombositemi, Primer miyelofibroz, Kalretikulin

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Address for Correspondence/Yazışma Adresi: Veysel Sabri HANÇER, M.D.,
İstinye University Faculty of Medicine, Department of Medical Genetics, İstanbul, Turkey
Phone : +90 533 634 30 14
E-mail : vshancer@yahoo.com **ORCID-ID:** orcid.org/0000-0003-2994-1077

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