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LETTER TO THE EDITOR

A novel nucleotide substitution in the 5′ untranslated region of *ANKRD26* gene is associated with inherited thrombocytopenia: a report of two new families

Robert T. Diep[1] · Kristin Corey[1] · Murat O. Arcasoy[1]

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Dear Editor,

Inherited thrombocytopenias (IT) constitute a rare etiology of thrombocytopenia and consist of a heterogenous group of hemostatic disorders caused by molecular defects in over 30 genes [1]. Approximately 18% of inherited thrombocytopenias are caused by monoallelic point mutations in ankyrin repeat domain 26 gene (*ANKRD26*), also termed thrombocytopenia-2 (THC2 OMIM 188000), with autosomal dominant transmission and increased predisposition for myeloid neoplasms [2]. We describe two IT cases presenting during pregnancy, one of whom harbored a novel, pathogenic nucleotide substitution in *ANKRD26* gene 5′ untranslated region (UTR).

Case 1 A 32-year-old woman was evaluated for chronic thrombocytopenia, platelet counts ranging from 39 to 50 × 10^9/L, associated with easy bruising. Thrombocytopenia had been recognized early during her first pregnancy at age 23, platelet count declining to 21 × 10^9/L during gestation, without response to high-dose corticosteroids and IVIG for presumptive diagnosis of immune thrombocytopenic purpura (ITP). Platelet concentrate transfusion was given prior to cesarean section to deliver a healthy baby boy. Bone marrow biopsy was normocellular at 70%, with myeloid:erythroid ratio at 3:1, and normal megakaryocyte number and morphology. At the current hematologic evaluation, platelet count was 43 × 10^9/L, and platelet size (MPV 11 fL) and morphology were normal. Family history revealed mild thrombocytopenia (90–100 × 10^9/L) in her brother, sister, and 8-year-old son who also exhibited easy bruising. Genetic analysis of *ANKRD26* revealed heterozygous mutation c.−118C>G in the 5′ UTR, a novel nucleotide substitution that has not been reported previously.

Case 2 A 71-year-old woman was evaluated for thrombocytopenia pre-operatively for elective knee replacement. She presented with thrombocytopenia during her first pregnancy at age 35 when she experienced post-partum bleeding requiring blood transfusions. A sternal bone marrow aspirate was reported normal and she was diagnosed with ITP. She reported easy bruising and rare self-limiting epistaxis over the years with platelets ranging from 40 to 50 × 10^9/L. A subsequent bone marrow biopsy reported normal megakaryocyte number and morphology. At age 64, she developed subarachnoid hemorrhage from a brain aneurysm and underwent endovascular coiling. Platelet counts declined to 23 × 10^9/L requiring platelet transfusions, but without sustained increment. There was no response to high-dose corticosteroids. Weekly romiplostim injections improved platelet count to 153 × 10^9/L within 12 days. The current hematologic evaluation was notable for platelet count 48 × 10^9/L, normal platelet size (MPV 10.1 fL), and normal platelet morphology. The patient's father had died of leukemia at age 52, a paternal aunt was diagnosed with leukemia at age 70, and chronic thrombocytopenia was noted in a paternal uncle, the patient's sister, and her sister's son and grandson who all exhibited easy bruising and carried the diagnosis of ITP. A paternal cousin had undergone splenectomy without response. Genetic evaluation for IT included *ANKRD26* mutation testing, demonstrating heterozygous variant c.−118C>T in 5′ UTR, reported previously in other unrelated families [3]. The patient's 32-year-old son had only mild thrombocytopenia (range 88–125 × 10^9/L, MPV 10.2 fL) and harbored the same mutation.

The recognition and diagnosis of IT in adults remain challenging. Many patients are initially diagnosed with ITP and may receive ineffective and potentially harmful treatments,

✉ Murat O. Arcasoy
murat.arcasoy@duke.edu

[1] Division of Hematology, Department of Medicine and Duke Cancer Institute, Duke University School of Medicine, Durham, NC 27710, USA

such as corticosteroids or splenectomy, as observed in our cases. Clinical features raising suspicion for IT include (1) non-response to prior immunosuppressive treatment for presumed ITP, (2) family history of thrombocytopenia, and (3) personal or family history of myeloid malignancy, especially in family members with antecedent thrombocytopenia. *ANKRD26*-related thrombocytopenia (*ANKRD26*-RT) should be considered in IT patients with (1) mild to moderate thrombocytopenia with normal platelet morphology and size [4]; (2) relatively mild bleeding manifestations; (3) apparent autosomal dominant inheritance pattern in the family; (4) absence of syndromic phenotypes such as skeletal, cardiovascular, and cognitive abnormalities or immunodeficiency; and (5) personal or family history of myeloid malignancy. Increased awareness and genetic diagnosis to confirm IT are important for avoidance of ineffective therapies, for genetic counseling, close hematologic follow-up, and screening prior to bone marrow donation from a family member to treat transformation to hematologic malignancy. Targeted analysis of a panel of IT genes is indicated to establish the diagnosis in affected individuals and family members with thrombocytopenia [2].

ANKRD26 encodes an inner cell membrane protein involved in protein-protein interactions with cytoskeletal and signaling proteins [1]. Pathogenic, monoallelic IT mutations primarily cluster in the 5′ UTR in a highly conserved, short sequence of nucleotides spanning from c.−140C to c.−116C, identified in more than 20 families [3, 5–10]. We introduce into the literature two new families with *ANKRD26*-RT, one of which harbor a novel nucleotide substitution c.−118C>G located within the 5'UTR. A mechanism for *ANKRD26*-RT was proposed in a recent study, demonstrating that in healthy individuals, *ANKRD26* expression is downregulated during normal megakaryopoiesis [11]. As a result of 5'UTR mutations in *ANKRD26*-RT, transcription factors *RUNX1* and *FLI1* fail to bind the mutated motifs to repress transcription, leading to sustained expression of *ANKRD26* during megakaryopoiesis. In turn, *ANKRD26* accumulation at the inner part of the cell membrane is associated with increased TPO/MPL signaling, abnormal activation of ERK, and impaired proplatelet formation leading to decreased platelet production. Germline mutations in *RUNX1* and *FLI1* have also been associated with IT [1, 2].

ANKRD26-RT predisposes affected individuals to the development of myeloid neoplasms, including acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia, and chronic myelomonocytic leukemia in about 8% of reported cases [2, 6, 9]. This propensity towards myeloid neoplasms may potentially involve upregulation of TPO/MPL and ERK signaling in hematopoietic cells [11]. The 2016 revision of the WHO classification of myeloid neoplasms and acute leukemias has introduced a new category defined as "myeloid neoplasms with germ line predisposition and preexisting platelet disorders," to include *ANKRD26*-RT and familial platelet disorder predisposing to acute myeloid leukemia caused by *RUNX1* mutations [12].

Management of *ANKRD26*-RT is similar to other ITs, with the vast majority of cases requiring no hematologic intervention. In the setting of clinically serious bleeding complications, the standard of care indicates supportive management, avoidance of drugs that impair platelet function, and platelet concentrates transfused to control hemorrhage or prior to major surgical procedures. Short-term treatment with thrombopoietin receptor agonist romiplostim resulted in normalization of platelet count in our patient in setting of subarachnoid hemorrhage to stabilize platelet count. Eltrombopag has been successfully used in a patient with *ANKRD26*-RT pre-operatively [13] and more extensively studied in *MYH9*-related IT [14]. However, long-term effects of these agents are not known and would raise potential concern in individuals with *ANKRD26*-RT with predisposition to hematologic transformation and development of myeloid neoplasms.

Compliance with ethical standards

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

Informed consent Informed consent was obtained from all individual participants in the study.

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