Non-consanguineous pediatric myelofibrosis due to MPIG6B mutations in a patient of European ancestry

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Abstract

Myelofibrosis (MF) in the pediatric setting is uncommon and appears to be pathogenically heterogeneous. MF due to intrinsic bone marrow abnormality (IMF) is distinct from adult-type Primary myelofibrosis (PMF) as they can lack the common genetic markers of clonality. To date, all but two reported patients with pediatric MF and mutated MPIG6B have been Arabic, and all reported cases have had a family history of consanguinity. Here we report the first North American patient of European ancestry with pediatric MF in whom novel compound heterozygous mutations of MPIG6B were identified.

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Pediatric myelofibrosis with *MPIG6B* mutations

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Abbreviations: IMF, intrinsic myelofibrosis; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; *MPIG6B* , megakaryocyte and platelet inhibitory receptor G6B; NGS, next generation sequencing; PMF, primary myelofibrosis; WES, whole exome sequencing

ABSTRACT

Myelofibrosis (MF) in the pediatric setting is uncommon and appears to be pathogenically heterogeneous. MF due to intrinsic bone marrow abnormality (IMF) is distinct from adult-type Primary myelofibrosis (PMF) as they can lack the common genetic markers of clonality. To date, all but two reported patients with pediatric MF and mutated*MPIG6B* have been Arabic, and all reported cases have had a family history of consanguinity. Here we report the first North American patient of European ancestry with pediatric MF in whom novel compound heterozygous mutations of *MPIG6B* were identified.

INTRODUCTION

Myelofibrosis in the pediatric setting is uncommon with secondary MF due to inflammatory, metabolic or infectious etiologies comprising most cases. MF due to an intrinsic bone marrow abnormality includes non-neoplastic, familial, and neoplastic cases. Primary myelofibrosis is a clonal myeloproliferative neoplasm most common in adults and characterized by megakaryocytic proliferation with atypia and myeloid proliferation, ultimately progressing to overt myelofibrosis (1). By contrast, IMF in the pediatric setting is pathogenetically heterogeneous (2). In comparison to adult PMF, in the three largest studies of pediatric IMF, *JAK2* V617F, *CALR* , or *MPL* W515L mutations were detected in 17% of patients, most of which were *CALR* mutations detected in a single study (2-5).

Multiple consanguineous families of Arabic ancestry have been described in which affected family members had IMF of variable severity together with anemia and thrombocytopenia (6-8). Genetic analyses of these kindreds have identified homozygous mutations in *MPIG6B* (*megakaryocyte and platelet inhibitory receptor G6B*), which encodes a megakaryocyte-specific cell surface receptor that contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) and appears to regulate megakaryocyte function and platelet formation (9, 10). The *MPIG6B* mutations identified include mRNA splice donor site, frameshift, and missense point mutations. Sometimes, these mutations result in the expression of a truncated MPIG protein and appear to cause significantly reduced expression of MPIG.

CASE REPORT

The patient is a 17-year-old white female of European ancestry and the product of a non-consanguineous pregnancy. She initially presented at age 2 with thrombocytopenia and anemia and was diagnosed with idiopathic thrombocytopenic purpura; however, her thrombocytopenia was poorly responsive to IVIG, WinRho, and steroids. Due to persistent thrombocytopenia, she underwent a splenectomy at 6 years. Although there was transient normalization of her platelet counts following splenectomy, her thrombocytopenia recurred with stabilization of the platelet count in the 30-40 x 109/L range. Therapy with eltrombopag was attempted at age 15 but discontinued due to leg pain. Her hemoglobin levels have ranged from 9-12 g/dL with low to normal MCV, absolute reticulocytosis, and elevated RDW (Figure 1E). Bilirubin, LDH, and iron studies were normal. Inherited hemolytic anemia and red blood cell membrane defect next generation sequencing (NGS) studies identified no pathogenetic mutations.

Bone marrow examinations were performed at 4, 15, and 17 years of age (Figure 1A). Moderate reticulin fibrosis (grade 2-3) was noted in all three biopsies. The initial two biopsies at 4 and 15 years of age were normocellular to slightly hypercellular, but the most recent showed hypocellularity.

Cytogenetics yielded a normal female 46, XX karyotype. FISH showed no evidence of a *BCR-ABL1* fusion or *KMT2A* (*MLL* ; 11q23) rearrangement and was negative for numeric and structural chromosomal abnor-

malities. Targeted NGS testing was negative with no evidence of *JAK2* , *MPL* , and *CALR* mutations. A variant of unknown pathogenic significance was identified in *SH2B3* (p.Ser213Arg).

Given the uninformative genetic studies, whole exome sequencing (WES) trio analysis was performed on the patient and her parents. This analysis identified in the patient a novel compound heterozygous mutation of *MPIG6B* and confirmed that the parents were each positive for one or the other of these mutations (Table 1, Figure 1B).

The patient's clinical course has been uneventful, with occasional fatigue, headaches, and prolonged and irregular menses. She has only received one red cell transfusion secondary to menorrhagia and has required no platelet transfusions. Given her stable condition, she is not currently considered a candidate for allogeneic bone marrow transplantation.

DISCUSSION

This report describes a patient with pediatric myelofibrosis due to underlying *MPIG6B* mutations (PM-MPIG6B). Novel compound heterozygous *MPIG6B* mutations were identified in our patient. To our knowledge is the first case of PM-MPIG6B to develop in a North American patient of western European ancestry without a family history of consanguinity. Nearly all reported cases (16/18) have occurred in patients of Arabic ancestry, all of whom were products of consanguineous marriages. Although rare, the current case confirms that PM-MPIG6B should be included in the differential diagnosis of any child with early-onset thrombocytopenia, anemia, and MF.

PM-MPIG6B was recently described in two independent analyses of 13 individuals of multiple consanguineous Arabic kindreds (7, 8). Affected individuals usually present in early childhood with variably severe anemia and thrombocytopenia, necessitating red cell or platelet transfusion in some patients. Splenomegaly is present in a subset of patients. Bone marrow examination typically reveals MF that is of variable severity. The phenotypic variability in PM-MPIG6B may reflect the extent to which the underlying mutation disrupts the expression or function of MPIG6B. There has been no report of transformation to acute leukemia or development of myeloid malignancy in patients with PM-MPIG6B.

MPIG6B is a conserved transmembrane protein that is highly and selectively expressed by megakaryocytes and platelets (10) (Figure 1B). The clinical and laboratory findings in PM-MPIG6B are phenocopied to a significant extent by genetically engineered Mpig6b-deficient mice in whom severe macrothrombocytopenia and a bleeding diathesis develop (9). Studies in Mpig6B-deficient mice suggest that loss of Mpig6b impairs proplatelet formation by megakaryocytes, thereby inhibiting the production of platelets (9-13). MPIG6B presumably operates via a similar mechanism in human megakaryocytes. Both mutations in our patient reside within the Ig domain of MPIG6B and thus may disrupt its interaction with heparan sulfate-containing proteins. Alternatively, these mutations may destabilize the encoded protein, resulting in reduced expression of MPIG6B, as observed with some MPIG6B mutants (7).

An intriguing feature of our case is that the most recent bone marrow biopsy showed marked hypocellularity, in contrast to the findings of previous bone marrow studies. This finding suggests that a subset of patients with PM-MPIG6B may progress to bone marrow failure. As with other reported cases of PM-MPIG6B, there has been no diagnostic evidence of malignancy in any of the bone marrows from our patient.

MF in the pediatric setting is uncommon, with secondary cases due to reactive, infectious, or metabolic etiologies comprising most cases. PMF accounts for a subset of the remaining IMF cases, which appear more pathogenetically heterogeneous than in adults and encompass a broad differential diagnosis. Mutations in *JAK2* , *MPL* , or *CALR* are detected in virtually all cases of adult-type PMF but only seen in a minority of pediatric IMF cases. Once secondary causes of MF have been excluded, the primary diagnostic considerations when confronted with myelofibrotic bone marrow from a young child include familial, non-neoplastic etiologies, *bona fide* neoplastic PMF, and other myeloid malignancies. Myelofibrosis is a prominent feature of acute megakaryoblastic leukemia, which develops almost exclusively in children 3 years or younger, and significant myelofibrosis is uncommon in other pediatric AML subtypes. Until the identification of mutations

in *VPS45* in some cases of infantile MF, non-neoplastic familial pediatric MF has mainly remained enigmatic. Infants with homozygous *VPS45* mutations typically present with severe neutropenia, have variable platelet counts with some platelet aggregation defects, and MF (14, 15). While MPIG6B mutations have been identified in some familial cases, the genetic basis for the remainder of familial MF cases is poorly understood. Hopefully, the application of genome wide NGS analyses will clarify the genetic basis of such cases. Thus, PM-MPIG6B should be considered in any patient with early-onset anemia and thrombocytopenia regardless of ethnicity or absence of a family history of consanguinity once common mutations associated with neoplastic or familial causes of MF have been excluded.

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Table 1.docx available at https://authorea.com/users/485503/articles/570868-non-consanguineous-pediatric-myelofibrosis-due-to-mpig6b-mutations-in-a-patient-of-european-ancestry