stem cell transplantation, since this might further increase the risk of infection. Conversely, these compounds may exert beneficial effects on alloreactivity (ie, graft-versus-host disease).

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To the editor:

**MYSM1** is mutated in a family with transient transfusion-dependent anemia, mild thrombocytopenia, and low NK- and B-cell counts

Several inherited bone marrow failure syndromes (IBMFSs) have been characterized, such as Fanconi anemia; however, about 1 in 4 IBMFS patients remain unclassified.1,2 Next-generation sequencing can be a powerful tool to identify novel genetic etiologies in patients with unclassified IBMFS, especially in the setting of consanguinity where the causal mutation usually resides within the easily tractable autozygome.3,4 This phenomenon narrows the candidacy of the large number of variants that are generated by next-generation sequencing, which makes it possible to identify the causal mutation even in simplex cases.5,6 Thus, the study of unclassified IBMFSs in Saudi Arabia where the consanguinity rate is high represents an opportunity to identify novel disease genes, and these may similarly contribute to the causation of IBMFSs in outbred populations.

We implemented this approach in 2 siblings with an apparently novel IBMFS and identified a homozygous truncating mutation in the **MYSM1** gene encoding MYB-like, SWIRM, and MPN domains-containing protein 1. Interestingly, these 2 siblings bear a striking resemblance to the phenotype of the **Mysm1**-null mouse that was published in **Blood.**7

Table 1. Laboratory characteristics of 2 siblings with a homozygous **MYSM1** mutation and comparison with the **Mysm1**-null mouse

<table>
<thead>
<tr>
<th>Laboratory characteristics</th>
<th>First patient</th>
<th>Second patient</th>
<th><strong>Mysm1</strong>-null mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (5000-15,000/µL)</td>
<td>3500</td>
<td>5400</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>4 y</td>
<td>7900</td>
</tr>
<tr>
<td>Hb (10.5-13.5 g/dL)</td>
<td>7.5</td>
<td>11.1</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>15 mo</td>
<td>3 y</td>
<td>9.8</td>
</tr>
<tr>
<td>MCV (77-85 fL)</td>
<td>83</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>11.5-14.5%</td>
<td>17.1</td>
<td>94</td>
</tr>
<tr>
<td>RDW (11.5-14.5%)</td>
<td>21.2</td>
<td>17.1</td>
<td>24.2</td>
</tr>
<tr>
<td></td>
<td>15 mo</td>
<td>3 y</td>
<td>25.1</td>
</tr>
<tr>
<td>Platelets (150,000-450,000/µL)</td>
<td>466 000</td>
<td>60 000</td>
<td>114 000</td>
</tr>
<tr>
<td></td>
<td>116 000</td>
<td></td>
<td>Increased</td>
</tr>
<tr>
<td>ALC (3000-10,000/µL)</td>
<td>2350</td>
<td>3670</td>
<td>4.34</td>
</tr>
<tr>
<td></td>
<td>15 mo</td>
<td>3 y</td>
<td>7000</td>
</tr>
<tr>
<td>ANC (1500-8500/µL)</td>
<td>690</td>
<td>1400</td>
<td>1.61</td>
</tr>
<tr>
<td></td>
<td>15 mo</td>
<td>3 y</td>
<td>500</td>
</tr>
<tr>
<td>Reticulocytes (1-3%)</td>
<td>0.69</td>
<td>0.54</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td>15 mo</td>
<td>3 y</td>
<td></td>
</tr>
<tr>
<td>CD3+ (1600-2700/µL)</td>
<td>3487</td>
<td></td>
<td>4684</td>
</tr>
<tr>
<td>CD4+ (1000-1700/µL)</td>
<td>1641</td>
<td></td>
<td>2736</td>
</tr>
<tr>
<td>CD8+ (600-1000/µL)</td>
<td>1508</td>
<td></td>
<td>1832</td>
</tr>
<tr>
<td>CD19+ (400-800/µL)</td>
<td>318</td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>CD16/CD56+ (200-400/µL)</td>
<td>86</td>
<td></td>
<td>69</td>
</tr>
<tr>
<td>IgA (0.25-1.54 g/L)</td>
<td>0.75</td>
<td></td>
<td>2.39</td>
</tr>
<tr>
<td>IgG (4.6-12.3 g/L)</td>
<td>6.96</td>
<td></td>
<td>6.06</td>
</tr>
<tr>
<td>IgM (0.43-1.96 g/L)</td>
<td>0.44</td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>IgE (1.5-114 IU/mL)</td>
<td>12.9</td>
<td></td>
<td>20.7</td>
</tr>
</tbody>
</table>

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; Hb, hemoglobin; MCV, mean corpuscular volume; RDW, red cell distribution width; WBC, white blood cell count.

References

The index is a 4-year-old girl who at 4 months of age developed pallor (hemoglobin was 6 g/dL) requiring blood transfusion. Physical examination revealed normal growth parameters, facial dysmorphism, and lack of hepatosplenomegaly. Chromosomal fragility test was normal. Serum ferritin, red blood cell folate, vitamin B₁₂ levels, and a metabolic screen were normal. Hemoglobin electrophoresis, direct antiglobulin test, and glucose-6-phosphate dehydrogenase level were also normal. She received monthly blood transfusions between 5 and 9 months of age. Bone marrow at 6 month of age was mildly hypocellular but otherwise unremarkable. Hemoglobin level improved after 9 months of age, and she became transfusion independent; however, platelets decreased to 60 000/μL by 4 years of age. Table 1 summarizes the laboratory results.

The second patient is the 3-year-old brother (supplementary Figure 1) who presented at the age of 15 months with pallor (hemoglobin was 4.4 g/dL). Physical examination and the course of the disease were similar to his sister. However, his requirement for monthly blood transfusion was more protracted, lasting until 33 months of age (Table 1). His bone marrow showed prominent erythropoiesis with reduced granulopoiesis and megakaryopoiesis, dysplastic erythroid precursors (internuclear chromatin bridging, binucleated, and megaloblastoid changes), and dysplastic megakaryocytes (small and hypolobated) with cellularity of 20% (supplementary Figure 2). The Ham test was negative.

With informed consent (King Faisal Specialist Hospital and Research Center Institutional Review Board Research Administration Council 2060008), we performed autozygosity mapping followed by exome sequencing of the index as described before. A single novel coding homozygous variant was identified in the shared autozygome of the 2 siblings (supplementary Figure 3): MYSM1:NM_001085487:exon8:c.1168G>T;p.E390*, which segregated with the disease phenotype within the family (supplementary Figure 1).

MYSM1 is a histone H2A deubiquitinase that was recently identified as a regulator of transcription.1 MySM1-null mice have compromised hematopoietic stem cells, anemia, thrombocytopenia, and lymphopenia as a result of increased oxidative DNA damage and increased expression of p53.2 MYSM1 is also required for early B-cell development by regulating the transcription of EBF1.3 The remarkable resemblance of the hematological phenotype between MySM1-null mice and our 2 patients suggests that the biallelic truncation of MYSM1 likely represents the cause of their IBMFS, although additional cases will be required to prove this causal link unequivocally.

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References


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To the editor:

Rare complete loss of function provides insight into a pleiotropic genome-wide association study locus

Recent genome-wide association studies (GWASs) of hematological traits have consistently found strong associations between the HBS1L-MYB intergenic region on 6q23 and a number of clinically significant hematologic traits, including fetal hemoglobin (HbF) levels, red blood cell counts and size, platelet counts, and white blood cell counts.1-4 Moreover, the variants in this locus have been shown to strongly affect the severity of sickle cell disease and thalassemia, emphasizing their clinical importance.5-7 The associated region is intergenic between 2 genes: HBS1L and MYB.1,2 Rare coding variants in MYB have been shown to be associated with HbF levels,2 whereas other evidence has suggested that variants in this region may affect HBS1L expression.8 Therefore, as is the case with
MYSM1 is mutated in a family with transient transfusion-dependent anemia, mild thrombocytopenia, and low NK- and B-cell counts

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