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Biallelic OSM deficiency presents with juvenile myelodysplastic syndrome and response to treatment

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Letter to the Editor **Genetics** **Hematology**

To the Editor: Garrigue et al. identified a biallelic variant in the human oncostatin M (OSM) gene in a consanguineous family (3 patients) with inherited severe bone marrow failure syndromes (IBMFS) in the patients aged from 10–20 years, with 4.4 years median age of onset, and in vitro and in vivo experiments established OSM roles in hematopoiesis (1). Similarly, we have identified three patients from 2 families with thrombocytopenia, anemia, and pancytopenia progressed to bone marrow failure with abnormal hematological values. Three affected females are homozygous for a loss-of-function variant (NM_020530.6: c.289C>T; Gln97Ter) in OSM (Figure 1A). They are aged between 17 years and 46 years, with the age of 14 being the disease onset median age, with a notable difference in the disease progression. The eldest patient (family 1; II:4) progressed to myelodysplastic syndrome (MDS), as she was suspected of having dyskeratosis congenita due to short telomeres requiring bone marrow transplant at the age of 40 years, with initial challenges due to transplant-related complications; however, the condition is stabilized with a successful outcome. This progression was not noted in family II (II:6 and II:9). It is worth noting the disorder may lead to MDS as the disease progresses. Remarkably, two patients (family II; II:6 and II:9) in our study have responded to eltrombopag and danazol with an increase in […]

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Remarkably, two patients (family II; II:6 and II:9) in our study have responded to eltrombopag and danazol with an increase in hemoglobin, white blood cells, and platelets (Figure 1B) from the seventh week of the treatment (Table 1). Our observation of eltrombopag response provides direct evidence of treatment for OSM deficiency. However, eltrombopag is an alternative to hematopoietic stem-cell transplantation (HSCT) in OSM deficiency and it, in turn requires a longer follow-up, and its mechanism needs to be investigated. Here, we reported three females with a founder variant with early truncation (Gln97Ter) in *OSM*. Hypothetically, early truncation can cause a severe phenotype; however, we noticed a late onset of disease in our patient. This could be because of IL-6 family genes sharing functional overlap with OSM (2). The findings from additional families (n = 3) with founder *OSM* variant establish the genotype-phenotype of *OSM* in bone marrow failure syndrome, elucidate the disease progression with a different age set of our patients, and enable us to propose a treatment option to avoid bone marrow transplantation.

Data availability. Clinical presentations are included in the supplemental material (Supplemental Table 1; supplemental material available online with this article; https://doi.org/10.1172/JCI192422DS1).

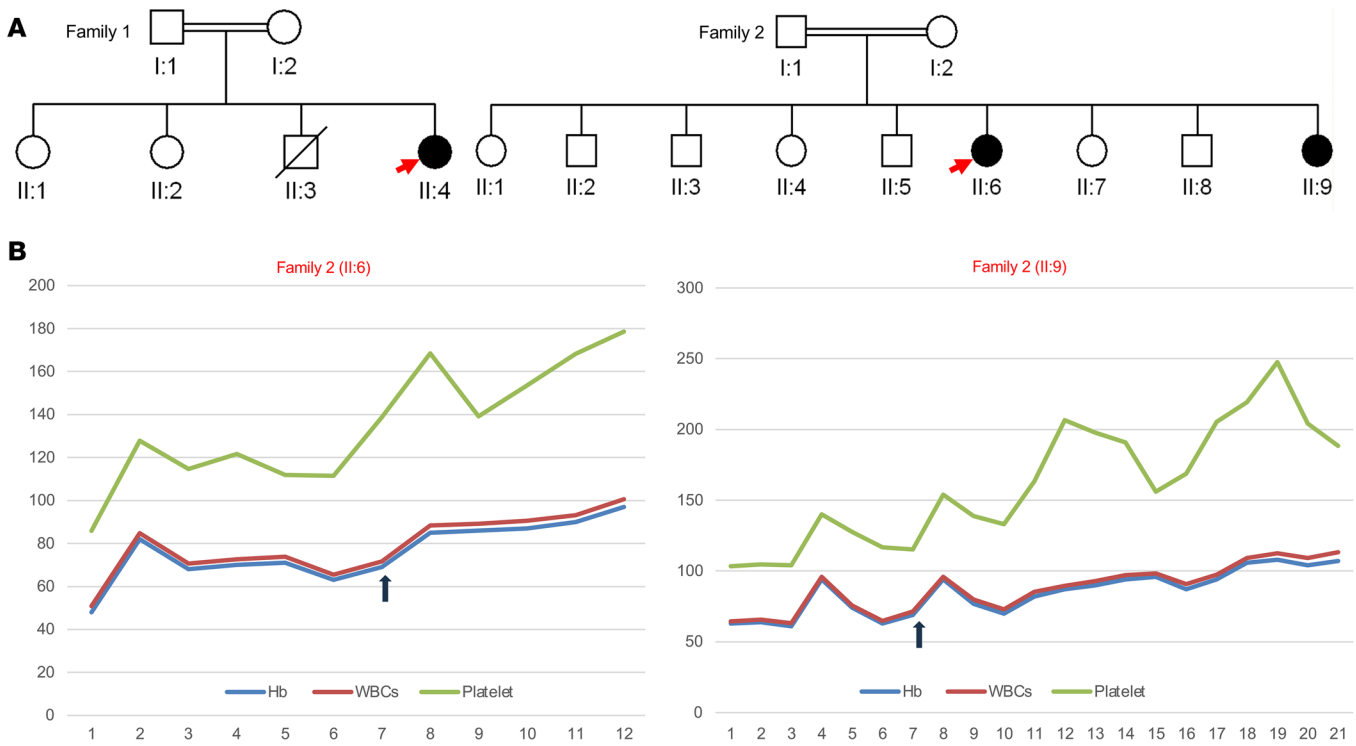

Figure 1. Response of OSM patients to eltrombopag. (**A**) Pedigree of the families. (**B**) Response of patients to eltrombopag (family 2; II:6 and II:7) from the seventh week.

Table 1. Clinical, molecular, and hematological characteristics of patients with pathogenic biallelic *OSM* variant

	Case 1 family 1 (II:4)	Case 2 family 2 (II:6)	Case 3 family 2 (II:9)
Age/Sex	47 years/female	24 years/female	17 years/female
Ethnicity	Arab (Saudi)	Arab (Saudi)	Arab (Saudi)
Age of diagnosis	25 years	12 years	5 years
Hematological presentations	Thrombocytopenia	Anemia	Pancytopenia
Molecular test	Exome sequencing	Exome sequencing	Exome sequencing
cDNA change (NM_020530.6)	c.289C>T	c.289C>T	c.289C>T
Amino acid change (NP_065391.1)	Gln97Ter	Gln97Ter	Gln97Ter
Genomic variant (NC_000022.10)	g.30660342G>A (hg19)	g.30660342G>A (hg19)	g.30660342G>A (hg19)
Treatment	Haplo-SCT	Eltrombopag	Eltrombopag and danazol
WBCs 10^9/L (3.90–11.00)			
Pre-Tx	2.50 (0.01–5.85)	2.34 (1.42–3.25)	2.81 (2.63–2.98)
Post-Tx	10.21 (0.01–47.87)	4.22 (3–6.34)	2.68 (1.16–4.58)
RBCs 10^{12}/L (3.90–4.60)			
Pre-Tx	2.67 (2.16–3.42)	2.708 (2.28–3.31)	2.73 (1.89–3.46)
Post-Tx	3.05(2.01–4.99)	3.166 (2.99–3.35)	2.875 (2.15–3.68)
Hb g/L (110–160)			
Pre-Tx	82.94 (70–101)	78 (61–94)	67.5 (48–85)
Post-Tx	90.25(56–144)	102.71 (96–108)	76.9 (58–97)
Hematocrit L/L (0.320–0.470)			
Pre-Tx	0.244 (0.205–0.292)	0.255 (0.201–0.313)	0.217 (0.156–0.275)
Post-Tx	0.275 (0.165–0.435)	0.330 (0.315–0.346)	0.245 (0.187–0.327)
Platelet 10^9/L (155–435)			
Pre-Tx	20.60 (1–157)	66.07 (35–117)	44 (35–49)
Post-Tx	113.13 (3–487)	100.42 (75–135)	60.5 (38–109)
Morphology	Reduced megakaryopoiesis, myelopoiesis and erythropoieses	Erythroid predominance with megaloblastoid	Trilineage maturation and relative paucity of myeloid precursors
BM cellularity	30%	50%–60%	50%
Cytogenetics/FISH	46,XX,t(10;13)dup(1)	46,XX	46,XX
Somatic NGS profile	NA	Negative	RUNX1:c.787C>T:p.P263S Allele frequency 43.2%
HLA-DRB1	DRB1*01:02 f, DRB1*13:01 f	DRB1*13:02 f, DRB1*15:01/204 f	DRB1*10:01/38Q, DRB1*07:01

Tx, treatment; Haplo-SCT: haploidentical cell transplantation; Hb, hemoglobin; NGS. next-generation sequencing.

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Conflict of interest: The authors have declared that no conflict of interest exists.

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