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Case series: Bone marrow failure in teen siblings with unique RPS19 variant

Alexandra Prosser
Children's Mercy Kansas City

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Alexandra Prosser, MD; Erin Hall, MD; Lauren Amos, MD

Children's Mercy Kansas City

Introduction

- Two siblings presented 2 weeks apart with severe pancytopenia and were both ultimately diagnosed with severe aplastic anemia (Table 1)
- Thorough exploration of possible infectious and environmental exposures unrevealing
- Unique *RPS19* variant in both siblings, but etiology remains unclear

Genetic evaluation

- *RPS19* is found on chromosome 19q13.2 and encodes ribosomal protein S19 (Fig. 1)[1]
- Three variants in 5' untranslated region (5' UTR) associated with Diamond-Blackfan anemia (DBA)[2]
- These cases present a unique heterozygous variant c.-163>T which substitutes a nucleotide in the noncoding exon 1 in 5' UTR
- Clinical presentation, with older age and lack of associated anomalies, not consistent with DBA

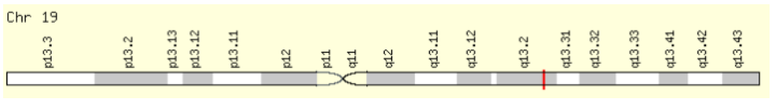

Figure 1

	CASE 1	CASE 2
Age/sex	13 YO F	16 YO M
Initial CBCd	WBC 1.83, ANC 160, Hgb 4.8, Plt 13	WBC 4.00, ANC 2190, Hgb 6.3, Plt 16
Bone marrow biopsy	Marked hypocellularity (0-10%) (Fig. 2)	Variable cellularity (10-70%) (Fig. 3)
Exposures	Previously took fluoxetine	Previously took fluoxetine
Genetics	*RPS19 variant* (c.- 163>T)	*RPS19 variant* (c.- 163>T)
Time to transplant	4 months	6 months
Donor type	MUD	MUD
Conditioning regimen	Fludarabine, Melphalan, Campath	Fludarabine, Melphalan, Campath

Table 1

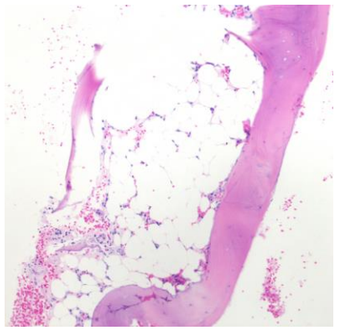

Figure 2: Case 1 initial bone marrow biopsy; H&E stain, x100; provided by Weijie Li, MD (CMH pathology)

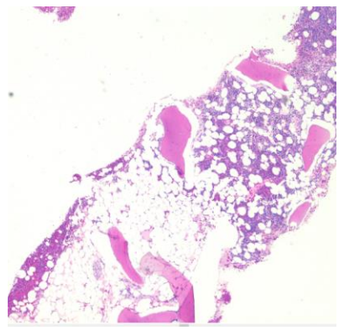

Figure 3: Case 2 initial bone marrow biopsy; H&E stain, x50; provided by Weijie Li, MD (CMH pathology)

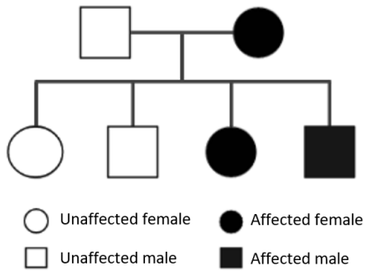

Figure 4

*Genetic testing of parents and siblings performed

*Their mother was also found to be heterozygous for the *RPS19* variant (Fig. 4)

*She is healthy with no history of medical issues

Management

- Both patients had sibling matches, who did not have the *RPS19* variant
- Due to possible unidentified genetic predisposition, proceeded with matched unrelated donors (MUD) rather than matched sibling donors for both patients
- Also utilized reduced intensity conditioning (Table 1)

Conclusion

- Unique presentation of bone marrow failure in siblings without known environmental exposures
- Potential novel pathogenic *RPS19* variant

References

1. "*RPS19* gene- ribosomal protein S19: Genomic view for RPS19 gene." www.genecards.org.
2. Cretien et al. "Genetic variants in the noncoding region of *RPS19* gene in Diamond-Blackfan anemia: Potential implications for phenotypic heterogeneity." *Am. J. Hematol*. 2010; 85:111-116.

UMKC School of Medicine

KU School of Medicine, The University of Kansas

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