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Variant of Unknown Significance in the EGLN-1 Gene Associated with Familial Erythrocytosis

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LSU Health SHREVEPORT

INTRODUCTION

- **Familial erythrocytosis** is a rare hereditary disorder leading to an abnormal **increase in red blood cell production** (1).
- **EGLN1** is a gene encoding for **prolyl hydroxylase domain-containing protein-2** (PHD2) which serves as an important factor within the **erythropoietin (EPO) regulatory pathway** and is a known gene implicated in familial erythrocytosis (3).
- Mutations in this gene can lead to **aberrant activation** of EPO and increased red blood cell production (2).
- Diagnosing erythrocytosis presents challenges, making it important to maintain **clinical suspicion** of a genetic component.

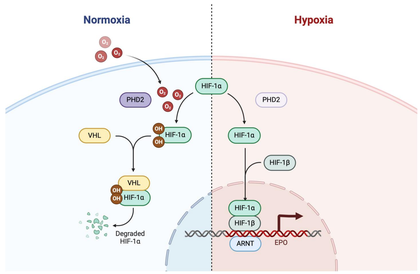


Figure 1. Adapted from "HIFSignalingPathway", by BioRender.com (2024). Retrieved from https://app.biorender.com/biorender-templates

CASE PRESENTATION

- A female in her 40's and her adolescent son presented with known polycythemia. Both had been receiving therapeutic phlebotomy every 2-4 weeks prior to presentation.
- Mother's past medical hx = polycythemia, hypertension, hyperlipidemia, morbid obesity (BMI 48.12), and obstructive sleep apnea
- Mother's social hx = cigarettes in the past (quit at age 29) but now vapes e-cigarettes
- Mother's family hx = polycythemia in mother
- Son's past medical hx = polycythemia

	Mother	Son
ABG pCO2 (nl 35-45 mmHg)	38 mmHg	---
Carboxyhemoglobin (nl <5%)	3%	---
C-reactive protein (nl <1 mg/L)	2.5 mg/L	---
Testosterone (nl 300-1000 ng/dL)	---	463 ng/dL
Erythropoietin (nl 4-26 mU/mL)	29 mU/mL	11.2 mU/mL
Hemoglobin variant	HbA 97.6%, HbA2 2.4%	HbA 97.7%, HbA2 2.3%

- JAK exon 12/13/14 and JAK2 V617F testing → negative
- Von Hippel-Lindau (VHL) related erythrocytosis or polycythemia testing → negative
- BPGM gene mutational testing → negative
- Additional familial erythrocytosis mutational testing → no definitive cause of hereditary erythrocytosis detected in the EGLN1 (PHD2), EPAS1 (HIF2A), or EPOR gene
- A **variant of uncertain significance (VUS) in the EGLN1 gene** was detected in both mother and son.
- The heterozygous VUS was found in EGLN1 gene (PHD2) as follows:

  Chr1(GRCh37): g.231556829A>G, c.806T>C, p.(Ile269Thr)

DISCUSSION

- Loss of function mutations in PHD2 can **decrease the hydroxylation** of proline residues in the α-subunit of the **hypoxia-inducible factor** (HIF) protein.
- Disruption of hydroxylation prevents von Hippel Lindau complex binding and **increases erythrocyte production.**
- One case of this mutation is reported as a variant of uncertain significance, along with three additional heterozygous individuals referred for erythrocytosis testing (Hgb 14.6-18.8 g/dL, Hct 41.7-53.6%) (4).
- There is a moderate physicochemical difference between **isoleucine** and the **threonine** that replaces it.
- The HIF2A gene was **incompletely sequenced**, which may indicate issues with primer binding or polymorphisms resulting in allelic drop out.
- In silico predictions suggest **potential impact on protein function**, but further evidence is needed to reclassify this variant as **pathogenic** or **benign** per ACMG guidelines.

CONCLUSION

- This variant within the EGLN1 gene **may disrupt** the balance of hypoxia-inducible factor (HIF) signaling, thus potentially leading to erythrocytosis.
- These findings highlight the need to **consider genetic factors** in diagnosing and managing familial erythrocytosis and prompts the need for **further research** into potential targeted therapeutic interventions.
- This case report contributes to the growing knowledge that may advance future direction in both diagnostic strategies and therapeutic interventions for individuals affected by this rare hematological disorder.

REFERENCES

1. McMullin MF. Idiopathic erythrocytosis: a disappearing entity. *Hematol Am Soc Hematol Educ Program*. Published online 2009:629-635. doi:10.1182/asheducation-2009.1.629
2. Percy MJ, Lee FS. Familial erythrocytosis: molecular links to red blood cell control. *Haematologica*. 2008;93(7):963-967. doi:10.3324/haematol.13250
3. Gardie B, Percy MJ, Hoogewijs D, et al. The role of PHD2 mutations in the pathogenesis of erythrocytosis. *Hypoxia Auckl NZ*. 2014;2:71-90. doi:10.2147/HP.S54455
4. Oliveira JL, Coon LM, Frederick LA, et al. Genotype-Phenotype Correlation of Hereditary Erythrocytosis Mutations, a single center experience. *Am J Hematol*. Published online May 23, 2018. doi:10.1002/ajh.25150

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The patient provided verbal informed consent to have their medical information published anonymously.