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Case Series

Genetic Analysis of Three Iranian Patients with Unexplained Absolute Erythrocytosis Using Customized Gene Panel Sequencing: A Case Series

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Abstract

Introduction: Erythrocytosis is a medical condition characterized by an increased mass of red blood cells, typically indicated by elevated levels of hemoglobin and hematocrit. This case series underscores the diagnostic challenge presented by unexplained absolute erythrocytosis in patients lacking canonical driver mutations and highlights the importance of utilizing extended gene panels to detect rare variants associated with erythropoiesis.

Case Report: Three Iranian patients exhibited absolute erythrocytosis, characterized by elevated hemoglobin and hematocrit levels, a normal erythropoietin concentration, and no history of smoking or chronic hypoxia. In addition, one female patient had coronary artery disease and mild hepatosplenomegaly, while the other two male patients were asymptomatic. Patients were referred from Ali Ebne Abitaleb Hospital in Zahedan to Dr. Kordi's Medical Genetics Laboratory in Zahedan for genetic assessments. Canonical genetic mutation analysis using Sanger sequencing revealed no mutations in hotspot regions of *JAK2*, *CALR*, and *MPL* (triple-negative). Therefore, targeted next-generation sequencing (NGS) was performed for these three patients using a customized 504-gene panel to identify potential genetic variants. After that, three rare missense variants were identified using a standard NGS analysis pipeline: NM_022162.3(*NOD2*):c.743T>G:p.Leu248Arg (rs104895423), NM_000402.4(*G6PD*):c.1039G>A:p.Glu347Lys (rs5030872), and NM_144658.3(*DOCK11*):c.2762G>A:p.Arg921Gln (rs2014585801). These variants were indexed as variants of uncertain significance (VUS) by the ClinVar and InterVar databases. Finally, variants were visualized using the Integrative Genomics Viewer (IGV) software.

Conclusion: These findings indicate that rare variants in our patients may contribute to unexplained absolute erythrocytosis.

Keywords: Polycythemia, Erythrocytosis, High-throughput nucleotide sequencing, Genetic variation

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Introduction

Erythrocytosis, also known as polycythemia, is diagnosed when hemoglobin or hematocrit values exceed the normal reference range.[1] This condition is subdivided into absolute and relative types. Absolute erythrocytosis is typically diagnosed when the red cell mass (RCM) exceeds 125% of the predicted value, a calculation that incorporates genetic and physiological variables such as body mass and gender.[1] In clinical practice, sex-specific thresholds are used for screening erythrocytosis, defined as "hemoglobin > 16.5 g/dL or hematocrit > 49% in males, and hemoglobin > 16.0 g/dL or hematocrit > 48% in females."[1, 2] Erythrocytosis is a relatively uncommon condition within the general population, with an estimated prevalence of about 0.38%, equivalent to about 383 cases per 100,000 individuals. A subset of these cases is identified as unexplained erythrocytosis, affecting roughly 0.04% of the general population, or approximately 40.8 cases per 100,000 individuals.[3]

Absolute erythrocytosis may result from primary causes, which involve intrinsic bone marrow abnormalities, often linked to genetic mutations, or from secondary causes, where external factors or inherited conditions outside the marrow stimulate increased red blood cell production.[4]

Also, other key conditions associated with absolute erythrocytosis include hypoxia-related factors such as high altitude exposure, carbon monoxide poisoning, pulmonary disorders, and high-affinity hemoglobins; splenomegaly; pharmacological influences from androgenic steroids; neoplasms such as hepatoma and

hypernephroma; renal complications like renal artery stenosis; polycythemia vera; Janus Kinase 2 (*JAK2*) genetic mutations, especially in p.V617F and exon 12; as well as hereditary erythrocytosis linked to erythropoietin (*EPO*) receptor mutations and Chuvash polycythemia.[5]

Janus kinase 2 (*JAK2*), calreticulin (*CALR*), and myeloproliferative leukemia protein (*MPL*) genes remain unmutated in rare cases of erythrocytosis, and differential genetic diagnosis should be performed using high-throughput sequencing techniques such as whole-exome sequencing (WES) or targeted next-generation sequencing (NGS) gene panels that include somatic clonal genes involved in hematological pathways.[6, 7] Identifying potential genetic variants in patients with erythrocytosis is crucial, as a subset of these individuals may be at risk of developing hematological neoplasms, such as acute myeloid leukemia, due to the gradual accumulation of clonal mutations in other genes over time.[8] Delic et al. research using a 28-gene panel demonstrated that DNA methylation genes had the greatest mutation frequency in polycythemia vera, although no mutations in splicing genes were identified in these patients.[9] Another study conducted by Camps et al. on individuals with idiopathic erythrocytosis using a 21-gene panel revealed that approximately 46% of patients had at least one of 51 detected mutations.[6]

Consequently, identifying genetic variants associated with isolated erythrocytosis requires the development of accurate and cost-effective genetic methods. We present three rare genetic variants in three Iranian patients with unexplained absolute erythrocytosis who did not have canonical mutations in *JAK2*, *CALR*, and *MPL* genes.

Case Presentation

Study Design

We report three Iranian individuals, one female and two males, from Zahedan who were apparently in good health and initially presented to their primary care physician at Ali Ebne Abitaleb Hospital in Zahedan, Iran, with non-specific symptoms including fatigue, blurred vision, dizziness, headaches, and hypertension. The patients had no history of chronic hypoxia, smoking, mental disorders, or genetic problems. While Patient 1 had a known history of coronary artery disease and exhibited mild hepatosplenomegaly on physical examination, Patients 2 and 3 were physically healthy with no significant findings.

Initial laboratory investigations, including a complete blood count (CBC), revealed an elevated hemoglobin and hematocrit above sex-specific reference ranges in all three patients, while red blood cell indices, serum erythropoietin (*EPO*) levels, and other blood components were within normal ranges (Table 1).

Based on these abnormal findings, the primary care physician referred them to an oncologist at Ali Ebne Abitaleb Hospital in Zahedan, Iran, for further evaluation. These three patients demonstrated elevated hemoglobin and hematocrit values above sex-specific reference ranges. None had a history of smoking or chronic hypoxia.

Upon oncologist assessment, the clinical presentation and laboratory profile raised suspicion of absolute erythrocytosis. To establish a differential diagnosis, particularly for myeloproliferative neoplasms such as

Table 1. Clinical, biochemical, and molecular characteristics of patients with isolated absolute erythrocytosis

Parameter	Patient 1	Patient 2	Patient 3	Reference range
Sex	Female	Male	Male	-
Age (years)	32	37	30	-
Hemoglobin (g/dL)	17.9	17	20	Male: 13-16 / Female: 12-15
Hematocrit (%)	55	53	60	Male: 38-51 / Female: 36-48
MCV (fL)	78	75	80	80-95
MCH (pg)	28	29	33	26-34
MCHC (g/dL)	30	30	31	32-36
RBC ($\times 10^9$/L)	5	5.1	5.5	Male: 4.2-5.8 / Female: 4-5.2
WBC ($\times 10^9$/L)	9	5.4	10	4.0-10.6
PLT ($\times 10^9$/L)	335	423	430	150-440
Oxygen level (%)	92	94	91	≥95
EPO (IU/L)	11	12	In the normal range[$]	4-26
Smoking	No	No	No	No
Other symptoms	Coronary artery disease and mild hepatosplenomegaly	None	None	-
JAK2 (V617F) mutation test	Negative	Negative	Negative	Negative
JAK2 (exon 12) mutation test	Negative	Negative	Negative	Negative
CALR (exon 9) mutation test	Negative	Negative	Negative	Negative
MPL (exon 10) mutation test	Negative	Negative	Negative	Negative

Note. $: The exact value is not available; M: Male; F = Female; MCHC: Mean Corpuscular Hemoglobin Concentration; MCH: Mean Corpuscular Hemoglobin; MCV: Mean corpuscular volume; PLT: Platelets; RBC: Red Blood Cells; EPO: Erythropoietin; WBC: White Blood Cells. The mutation analysis was performed using Sanger sequencing.

polycythemia vera, the oncologist referred the patients to Dr. Kordi's Medical Genetics Laboratory in Zahedan, Iran. Routine genetic screening for hotspot mutations in *JAK2* (V617F and exon 12), *CALR* (exon 9), and *MPL* (exon 10) was performed using Sanger sequencing of PCR products at Niagene Noor Company in Tehran, Iran. These genetic tests returned negative for all three patients, leading to a diagnosis of unexplained (idiopathic) absolute erythrocytosis (Table 1).

Following this diagnosis, management included prescribing low-dose aspirin for each patient. Subsequently, a next-generation sequencing (NGS) panel was employed to investigate other genes that may be implicated in hereditary or acquired erythrocytosis.

The study protocol was approved by the Research Ethics Committee of the University of Sistan and Baluchestan (Approval ID: IR.USB.REC.1402.035), and informed consent was obtained from all patients.

Next-Generation Sequencing Test

We developed a customized gene panel based on the 2024 update of the International Union of Immunological Societies (IUIS) classification of Inborn Errors of Immunity (IEI)[10] to explore potential genetic causes of unexplained absolute erythrocytosis. Our NGS panel included 504 genes engaged in immune regulation, hematopoiesis, and cytokine signaling.

First, genomic DNA was extracted from peripheral blood samples. Then, library preparation was carried out using the TruSeq Custom Amplicon panel (Illumina Inc., USA). Afterward, sequencing was performed on the NextSeq 2000 platform (Illumina Inc., USA) in paired-end mode (2 × 100 bp).

Raw sequencing data (FASTQ files) were quality controlled, trimmed, and mapped to the GRCh37/hg19 reference genome using a standardized command-line bioinformatics pipeline. After that, variant calling and annotation were performed using the Genome Analysis Toolkit (GATK) [version 4.6.2.0][11] and ANNOtate VARiation (ANNOVAR),[12] respectively. Then, identified variants were prioritized according to the American College of Medical Genetics and Genomics (ACMG) guidelines.[13] Ultimately, Integrative Genomics Viewer (IGV) version 2.19.4 was used to visually confirm candidate variants in the Binary Alignment/Map (BAM) files.

Genetic Findings

The bioinformatics pipeline identified rare missense variants in three genes: Nucleotide-Binding Oligomerization Domain-Containing Protein 2 (*NOD2*), Glucose-6-Phosphate Dehydrogenase (*G6PD*), and Dedicator Of Cytokinesis 11 (*DOCK11*). Details of variant annotation, *in silico* pathogenicity predictions, and population frequency data are provided in Table 2.

All variants were classified as Variants of Uncertain Significance (VUS) according to ACMG criteria. Briefly, Patient 1 presented with a heterozygous *NOD2*:c.743T > G:p.Leu248Arg (rs104895423) variant that is associated with "Blau syndrome (OMIM: 186580)." Patient 2, a 37-year-old male, presented with a hemizygous *G6PD*:c.1039G > A:p.Glu347Lys (rs5030872) variant that is linked to "G6PD deficiency (OMIM: 300908)." Patient 3 presented with a hemizygous *DOCK11*:c.2762G > A:p.Arg921Gln (rs2014585801) variant that is associated with "autoinflammatory disease, multisystem, with immune dysregulation, X-linked (OMIM: 301109)." The presence of each candidate variant was verified by evaluating BAM files with IGV. Snapshots from the IGV for the *NOD2*, *G6PD*, and *DOCK11* variants are shown in Figures 1–3, respectively.

In addition, the correlation between the expression levels of *JAK2*, *CALR*, *MPL*, *NOD2*, *G6PD*, and *DOCK11* genes is estimated using the GTEx database's multi-gene query (Figure 4).

Discussion

Our study introduces three immunological genes—*NOD2*, *G6PD*, and *DOCK11*—that have not been previously linked to the development of absolute erythrocytosis. Moreover, the roles of *NOD2* and *DOCK11* in erythropoiesis remain underexplored and warrant further investigation. Additionally, the frequency of these identified variants was very rare and not typically seen in healthy populations (Table 2).

A 2017 study in the United States involving 223 patients with myeloid neoplasms that used WES. This study applied a custom gene panel comprising 160 autophagy-associated genes and identified several variants in 40 patients. Notably, four variants were identified in the *NOD2* gene, which were three somatic (c.353A > G, c.3022G > T, and c.3023A > G) and one germline (rs104895423). This *NOD2* germline variant (rs104895423) is consistent with our finding for patient 1.[14]

G6PD plays a crucial role in protecting RBCs from oxidative stress; when this gene is deficient, it can lead to multiple hematological conditions, including hemolytic anemia.[15]

Nonetheless, a study reported that erythropoiesis in healthy individuals may be identical to that in patients with *G6PD* mutations.[16] However, our findings for Patient 2 suggest that a *G6PD* mutation may also be associated with erythrocytosis.

The hemizygous *DOCK11*:c.2762G > A:p.R921Q variant in Patient 3, supported by GTEx co-expression with *JAK2* (Figure 4), and recent evidence linking *DOCK11* to immune dysregulation.[17] A recent study utilizing WES identified a hemizygous nonsense mutation in *DOCK11* (c.3754C > T:p.Q1252*), resulting in a full absence of *DOCK11* expression, which is linked to immunodeficiency and inflammation.[18]Also, research has found that *DOCK11* mutations may cause erythropoietic diseases by influencing some factors, such as $CD34^+$cells.[19] This aligns with findings that immune pathways contribute to MPNs.[20]

Co-expression analysis from the GTEx project revealed that canonical erythrocytosis-associated genes clustered

Table 2. Details of genetic variations and *in silico* prediction of their pathogenicity

	Patient 1 (female)	**Patient 2 (male)**	**Patient 3 (male)**
Genes	***NOD2***	***G6PD***	***DOCK11***
Genomic position (GRCh37/hg19)	chr16:50744565 T>G	chrX:153761259 C>T	chrX:117742204 G>A
dbSNP build 151 or 157 ID	rs104895423	rs137852339	rs2014585801
Transcript change	NM_022162.3:exon4:c.743 T>G	NM_000402.4:exon9:c.1039 G>A	NM_144658.3:exon26:c.2762 G>A
Protein Change	p.Leu248Arg (L248R)	p.Glu347Lys (E347K)	p.Arg921Gln (R921Q)
Variant Type	missense	missense	missense
Zygosity	Heterozygous	Hemizygous	Hemizygous
ClinVar classification	Conflicting interpretations	VUS	VUS
InterVar classification	VUS	VUS	VUS
ACMG Classification	PM2, PP3, BS2	PM2, PP3, PS1	PM2, PP3
gnomAD v2.1.1 or v4.1.1 (exome)	0.0006	0.0012	9.16e-7
gnomAD v2.1.1 or v4.1.1 (genome)	0.0002	4.565e-05	Not reported
GERP++_RS	5.2 (High constraint)	5.53 (High constraint)	3.95 (Medium constraint)
SIFT	0.0 (Damaging)	0.001 (Damaging)	0.197 (Tolerated)
PolyPhen-2 (HDIV)	1.0 (Probably damaging)	0.837 (Probably damaging)	0.206 (Benign)
MutationTaster	Disease-causing (0.999989)	Disease-causing (0.999999)	Tolerated (0.61244)
DANN	0.91255 (Likely deleterious)	0.78490 (Borderline)	0.98 (Likely deleterious)
PROVEAN	-4.29 (Deleterious)	-3.74 (Deleterious)	-0.86 (Neutral)
REVEL	0.853 (Likely pathogenic)	0.648 (Possibly pathogenic)	0.124 (Likely benign)
CADD Phred	25.9 (Highly deleterious)	19.48 (Near threshold)	20.6 (Likely deleterious)
Associated Condition	Blau syndrome (OMIM: 186580)	Anemia, congenital, nonspherocytic hemolytic, 1, G6PD deficient (OMIM: 300908)	Autoinflammatory disease, multisystem, with immune dysregulation, X-linked (OMIM: 301109)
Inheritance Pattern	Autosomal dominant	X-linked recessive	X-linked recessive

Note. VUS: Variant of Uncertain Significance; gnomAD: Genome Aggregation Database (v.2.1.1 based on GRCh37; v.4.1.1 based on GRCh38); ACMG: American College of Medical Genetics and Genomics; GERP++_RS: Genomic Evolutionary Rate Profiling (Rejected Substitutions); SIFT: Sorting Intolerant From Tolerant; PolyPhen-2 (HDIV): Polymorphism Phenotyping v2 (High-Diversity Training Set); DANN: Deleterious Annotation of genetic variants using Neural Networks; PROVEAN: Protein Variation Effect Analyzer; REVEL: Rare Exome Variant Ensemble Learner; CADD Phred: Combined Annotation Dependent Depletion (Phred-scaled); dbSNP: Single Nucleotide Polymorphism Database; OMIM: Online Mendelian Inheritance in Man.

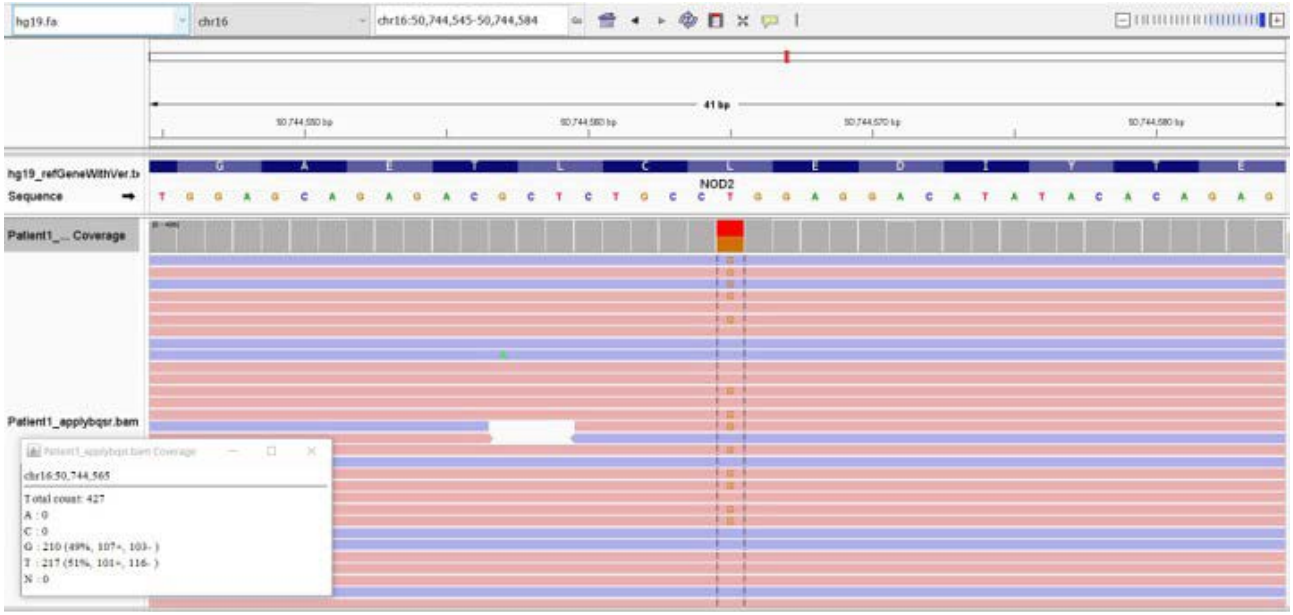

Figure 1. Visualization of *NOD2* genetic variation (NM_022162.3:exon4:c.743T>G:p.Leu248Arg, rs104895423) in Patient 1 using IGV software. The GRCh37/hg19 genomic location of the variant, chr16:50744565 T>G, is marked by a rectangle across the entire reads of the BAM file. The altered allele (G) can be observed in approximately half of the reads (210/427, 49%) of forward (pink) and reverse (blue) strands. Hence, the zygosity of the variant is heterozygous in this female patient. IGV: Integrative Genomics Viewer; BAM: Binary Alignment/Map

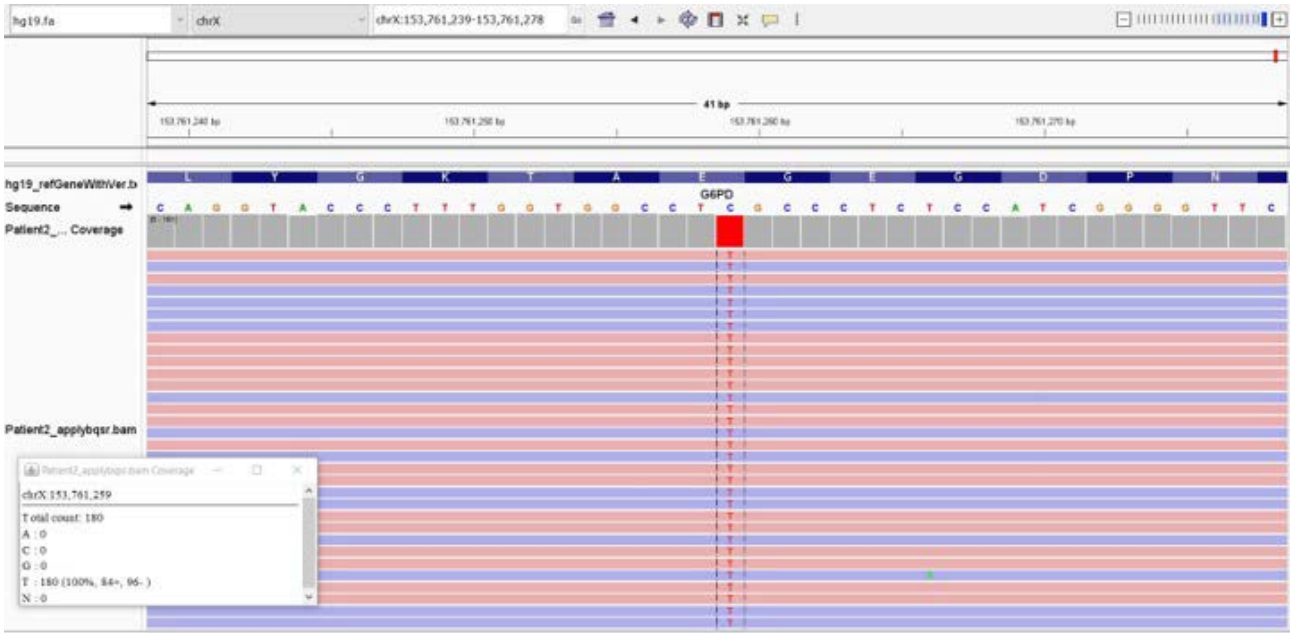

Figure 2. Visualization of *G6PD* genetic variation (NM_000402.4:exon9:c.1039G>A:p.Glu347Lys, rs137852339) in Patient 2 using IGV software. The GRCh37/hg19 genomic location of the variant, chrX:153761259 C>T, is marked by a rectangle across the entire reads of the BAM file. The altered allele (T) can be observed in all reads of (180/180, 100%) forward (pink) and reverse (blue) strands. This male patient has a variant on the X chromosome, making the zygosity hemizygous. IGV: Integrative Genomics Viewer; BAM: Binary Alignment/Map

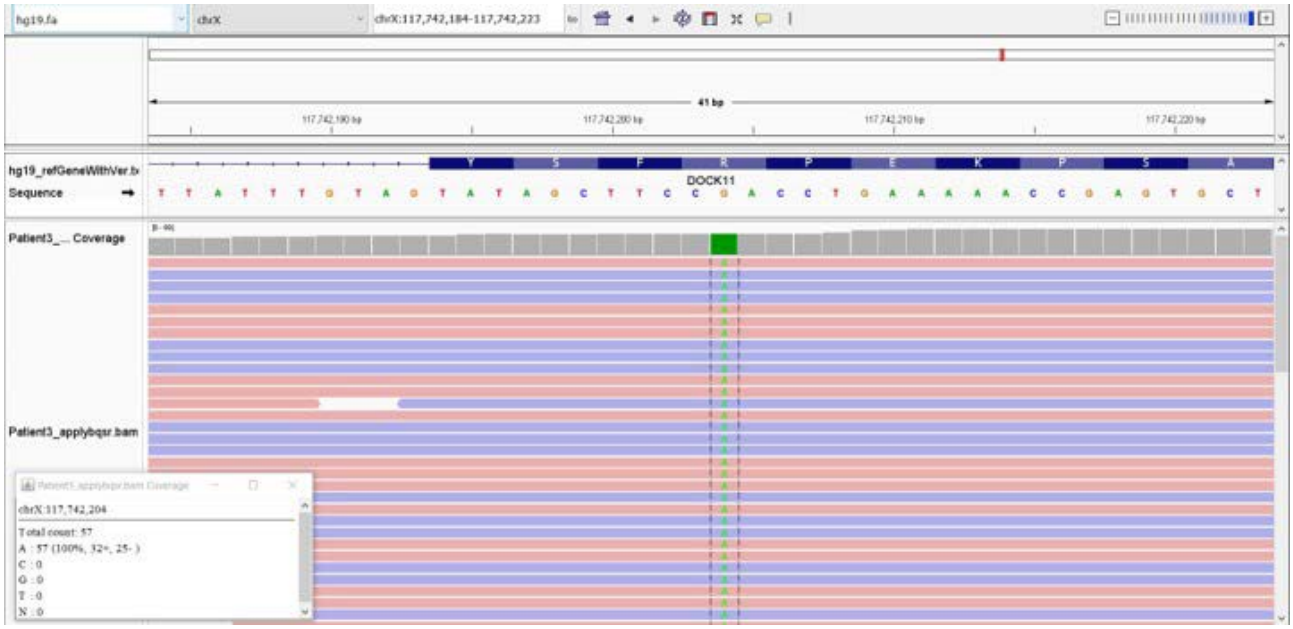

Figure 3. Visualization of *DOCK11* genetic variation (NM_144658.3:exon26:c.2762G>A:p.Arg921Gln, rs2014585801) in Patient 3 using IGV software. The GRCh37/hg19 genomic location of the variant, chrX:117742204 G>A, is marked by a rectangle across the entire reads of the BAM file. The altered allele (A) can be observed in all reads (57/57, 100%) of forward (pink) and reverse (blue) strands. This male patient has a variant on the X chromosome, making the zygosity hemizygous. IGV: Integrative Genomics Viewer

with the candidate genes identified in our patients. *JAK2* established a clade with *DOCK11*, *CALR* clustered with *G6PD*, and *MPL* associated with *NOD2*. These associations imply common transcriptional regulation or functional convergence among hematopoietic and immune-related tissues. Although *JAK2*, *CALR*, and *MPL* are recognized as primary drivers of myeloproliferative neoplasms, their associations with *DOCK11*, *G6PD*, and *NOD2* reinforce the hypothesis that these non-classical genes may influence erythropoietic regulation through intersecting pathways. These findings enhance the probability that rare variants in *DOCK11*, *G6PD*, and *NOD2* may influence red cell production, despite their current classification as variants of uncertain significance. Integrating GTEx-derived co-expression data with clinical sequencing results may provide significant biological context, informing future functional studies and prioritizing candidate variants in unexplained erythrocytosis.

While targeted panel sequencing offers significant advantages in terms of time and cost efficiency, it may not capture certain upstream or downstream genes that could indirectly influence erythrocytosis-related pathways.

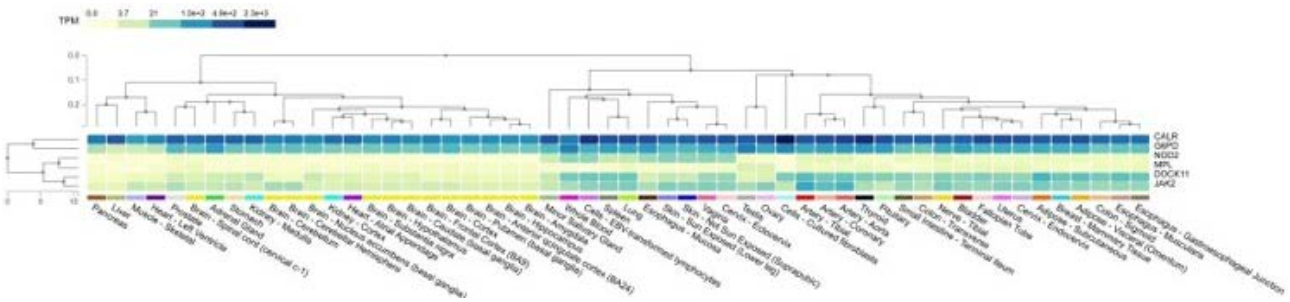

Figure 4. Analysis of RNA-seq data of the GTEx database across various human tissues to evaluate the possible co-expression of identified genes (*NOD2*, *G6PD*, and *DOCK11*) in our patients and canonical driver genes (*JAK2*, *CALR*, and *MPL*) of absolute erythrocytosis. This illustration was obtained from the Multi-Gene Query section of the GTEx database (https://gtexportal.org/home/multiGeneQueryPage). GTEx: Genotype-Tissue Expression; TPM: transcripts per million

Consequently, for patients with negative panel results, future studies should consider employing whole-exome sequencing (WES) to ensure broader genomic coverage. Additionally, Sanger sequencing confirmation was not performed for the identified variants in this study. However, variants demonstrated exceptionally high-quality metrics [*G6PD*:c.1039G > A:p.E347K (QUAL: 6132.06); *NOD2*:c.662T > G:p.L221R (QUAL: 5022.64); and *DOCK11*:c.2762G > A:p.R921Q (QUAL: 2116.06)] that far exceed commonly accepted thresholds. These values provide strong computational evidence supporting the reliability of the variant calls.

Conclusion

In this study, we identified three rare mutations in patients with isolated erythrocytosis. Given that these variants are classified as VUS by the ACMG guidelines, further functional studies are warranted to assess their biological and clinical implications in patients with erythrocytosis. However, our results may help clarify the role of immune-related genes in erythrocytosis, particularly in cases where canonical somatic mutations are negative.

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Authors' Contribution

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Supervision: Dor Mohammad Kordi-Tamandani, Seyed Mehdi Hashemi.
Validation: Dor Mohammad Kordi-Tamandani, Milad Mollaali, Seyed Mehdi Hashemi.
Visualization: Milad Mollaali.
Writing–Original Draft: Milad Mollaali.
Writing–Review & Editing: Dor Mohammad Kordi-Tamandani, Seyed Mehdi Hashemi, Milad Mollaali.

Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

The study protocol was approved by the Research Ethics Committee of the University of Sistan and Baluchestan (Approval ID: IR.USB.REC.1402.035), and informed consent was obtained from all patients.

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