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Comprehensive gene expression analysis of Polycythemia: Unveiling molecular pathways and therapeutic targets through multi-database integration

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Abstract

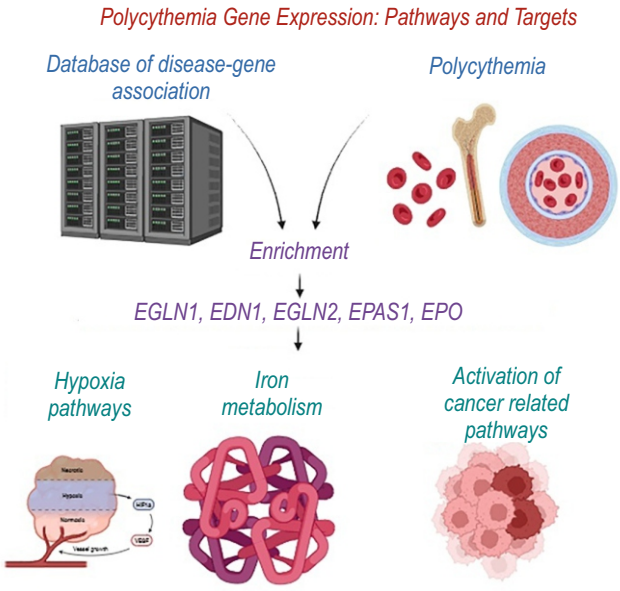
Aim: Polycythemia is a complex haematological disorder characterised by excessive red blood cell production, yet its underlying genetic mechanisms remain inadequately understood. This study sought to comprehensively explore the genetic landscape of polycythemia through integration of multiple bioinformatic database resources.

Methodology: The top 30 genes associated with polycythemia were retrieved from DisGeNET and analysed using Gene Ontology, WikiPathways, ClinVar, ChEA, TargetScan, DrugMatrix, HMDB, and Jensen databases. Functional enrichment, metabolite association, and drug interaction analyses were performed, with statistical analysis and visualisation conducted in R (v4.4.2).

Results: Fourteen genes, including *EGLN1, EPAS1, EPO, HIF1A, EPOR, VHL* and *JAK2,* demonstrated significant enrichment in hypoxia-inducible factor signalling pathways ($p < 0.001$). Key molecular processes identified encompassed iron metabolism, erythropoietin signalling and oxygen sensing. Metabolite analysis implicated ascorbic acid, hydroxyproline, iron, and L-proline, whilst drug interaction profiling highlighted metabolic and anti-inflammatory modulators as potential therapeutic targets.

Interpretation: This integrative analysis underscores the central roles of hypoxia response and iron metabolism in polycythemia pathophysiology. The identified metabolites and druggable targets offer novel insights that may inform therapeutic intervention and support the development of personalised treatment strategies.

Key words: Erythropoietin signaling, Gene expression analysis, Hypoxia-inducible factor, Iron metabolism, Polycythemia



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Introduction

Polycythemia can be considered as a heterogeneous group of hematopoietic disorders characterised by abnormal increase in red blood cell mass, that results in elevated hemoglobin and hematocrit levels (Tefferi *et al.,* 2021). Broadly, this condition has been classified into primary and secondary forms. Primary polycythemia, of which polycythemia vera stands as the most notable example, arises due to intrinsic abnormalities that occur within the hematopoietic stem cells whereas secondary polycythemia may result from diverse pathophysiological processes, including chronic hypoxia or inappropriate erythropoietin production (Viswanathan *et al.,* 2025). The clinical implications of polycythemia extend far beyond what can be considered as hematological alterations alone. Patients suffering from this condition often face serious complications which include cardiovascular disease, thrombotic events, and in certain cases progression toward myelofibrosis or even transformation into acute leukemia, and this underscores the necessity for early detection, close monitoring, and therapeutic interventions that are targeted (Tashkandi and Younes, 2024).

At molecular level, one of the central mechanisms which drives polycythemia involves the Janus kinase 2 (JAK2) signaling cascade. Under physiological conditions, erythropoietin abbreviated as EPO, binds to its receptor known as EPOR and this initiates JAK2-mediated signal transduction which ensures the survival, proliferation, and differentiation of erythroid progenitor cell (Abraham *et al.,* 2024). However, in case of polycythemia vera, somatic mutations in JAK2, most notably the JAK2 V617F mutation, disrupt this process which is otherwise tightly regulated. This particular mutation is detected in approximately 95% of polycythemia vera cases which results in the constitutive activation of erythropoietin signaling, thereby driving erythrocytosis independent of normal physiological control mechanisms (Regimbeau *et al.,* 2022). Such aberrant signals provide a critical pathogenic insight that has become a cornerstone in diagnostic strategies as well as serving as a therapeutic target in current clinical practice.

Iron metabolism also appears to play a pivotal role in modulating erythropoiesis and overall red blood cell production. Because availability of iron determines the efficiency with which hemoglobin synthesis occurs, disruptions in iron regulation directly impact the progression of polycythemia. Dysregulation of iron homeostasis, particularly involving regulatory proteins such as transmembrane protease serine 6 abbreviated as TMPRSS6, aconitase 1 abbreviated as ACO1, and transferrin receptor abbreviated as TFRC can alter iron sensing and utilization, and thereby contribute to polycythemic phenotypes (Ganz *et al.,* 2023). Furthermore, iron metabolism intersects with hypoxia signaling pathways, creates a complex regulatory network that governs cellular adaptation to oxygen fluctuations and metabolic demands (Lee *et al.,* 2020). This dynamic interplay adds another layer of intricacy to the biology of polycythemia and emphasizes the multifactorial nature that characterises its pathogenesis.

Despite considerable progress in identifying molecular contributors such as JAK2 mutations and iron-regulatory pathways, comprehensive integrative studies have remained limited. The field has not yet fully exploited large-scale, systems-level approaches that combine genomics, transcriptomics, metabolomics, and pharmacological datasets together. Such integrative strategies are essential not only for discovering novel therapeutic targets but also to address disease heterogeneity, refine diagnostic markers, and enable development of individualised treatment frameworks. Recent emergence of expansive bioinformatics tools and genomic databases presents an unprecedented opportunity to map the intricate molecular landscape of polycythemia. By integrating multiple layers of biological data, researchers may build a holistic framework that advances both mechanistic understanding and translational applications.

The present study has been designed keeping four primary objectives in view. First, to employ bioinformatics databases in performing functional enrichment analyses that highlight and characterise key genes which are associated with polycythemia. Second, to elucidate underlying biological processes and molecular pathways, particularly those which are linked to iron metabolism, erythropoietin signaling and hypoxia responses as these collectively shape disease pathophysiology. Third, to investigate drug interactions and metabolite associations with genes related to polycythemia, thereby identifying potential biomarkers and therapeutic candidates. Finally, to construct a comprehensive molecular framework that captures disease heterogeneity and may provide a basis for personalized therapeutic strategies in polycythemia. Collectively, this approach seeks to bridge molecular insights with clinical applications, and ultimately improve patient outcomes through precision medicine.

Materials and Methods

Genes showing association with polycythemia were extracted from the DisGeNet database (Piñero *et al.,* 2017) and were subjected to a series of downstream analyses. Functional enrichment was conducted by using updated 2023 Gene Ontology databases, abbreviated as GO. GO_ Biological_ Process_2023 identified the physiological and cellular processes in which polycythemia genes participate, and these included signaling pathways and regulatory mechanisms. GO_Cellular_Component_2023 highlighted patterns of subcellular localisation, while GO_Molecular_Function_2023 provided insights into specific biochemical activities and interactions of proteins that are encoded (Kuleshov *et al.,* 2016).

Pathway-level insights were obtained through WikiPathways_2024_Human, which revealed biological pathways that were significantly enriched. Hypergeometric testing with Benjamini–Hochberg correction was applied, and adjusted p-values below 0.05 were considered as significant. Integration with ClinVar_2019 identified variants that are clinically

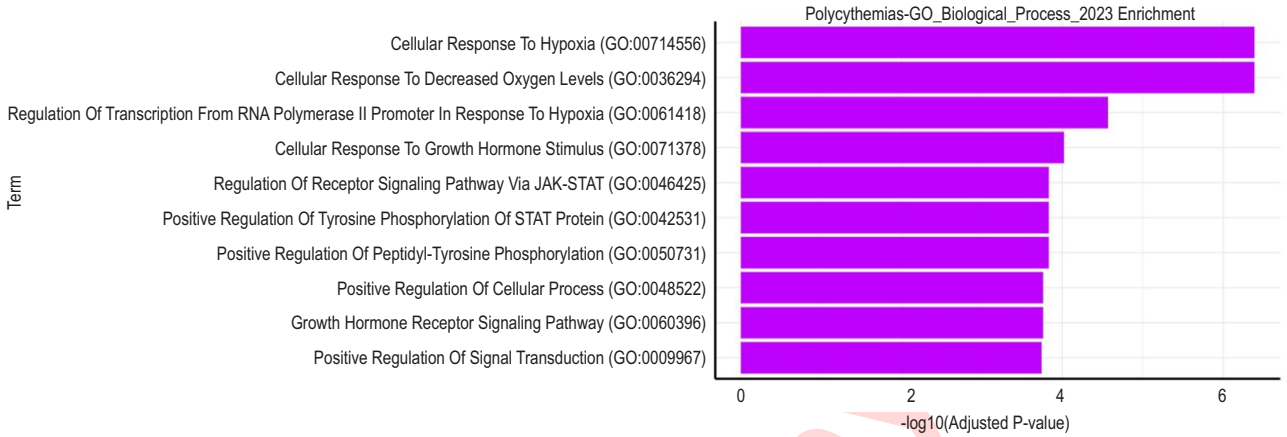

Fig. 1: Gene Ontology (GO) Biological Process enrichment analysis of polycythemias. The bar plot illustrates the top significantly enriched GO biological process terms which are associated with genes related to polycythemia, this being from 2023 dataset. The x-axis represents minus log base 10 of the p value and this indicates the significance level of enrichment, while the y-axis lists the corresponding enriched terms.

relevant, while data obtained from the Cancer Cell Line Encyclopedia enabled examination of expression patterns in hematological malignancies. Regulatory network exploration utilised ChEA_2022 to detect transcription factors potentially governing polycythemia genes, and TargetScan_ microRNA_ 2017 (Min and Yoon, 2010) predicted regulation that is microRNA-mediated. To capture metabolic and therapeutic dimensions, HMDB_Metabolites (Wishart *et al.,* 2007) provided associations with metabolites, whereas DrugMatrix identified pharmaceutical compounds that were capable of modulating genes linked to polycythemia, and this highlighted opportunities for biomarker discovery and drug repurposing. Tissue-specific expression and compartment-specific expression were assessed by Jensen_TISSUES and Jensen_COMPARTMENTS, and this complemented disease association mapping through Jensen_DISEASES, which uncovered comorbidities and shared pathological pathways. All statistical analyses were performed in R version 4.4.2 along with bioinformatics packages. Hypergeometric testing with false discovery rate adjustment was applied, alongside calculation of odds ratios and combined scores. Results were visualised through plotting functions based on R, and these generated detailed figures of enrichment, pathways and interaction networks. Statistical significance was set at p value < 0.05 following correction for multiple testing.

Results and Discussion

The comprehensive analysis of 30 genes associated with polycythemia revealed significant functional enrichment across multiple biological domains, and this provided detailed insights into molecular mechanisms which underlie this hematological disorder. The GO_Biological_ Process_2023 analysis (Fig. 1) demonstrated significant enrichment of genes, which are involved in oxygen sensing and response pathways, with particular emphasis being placed on cellular responses to hypoxia and oxygen levels. The biological processes that were most prominently represented included erythrocyte development and differentiation, hematopoietic stem cell differentiation, and regulation of transcription in response to hypoxia. These findings highlight the central role that oxygen homeostasis plays in pathogenesis of polycythemia, with multiple genes contributing to cellular adaptation mechanisms under varying oxygen conditions. The enrichment of transcription in response to hypoxia is mechanistically consistent with the well-established role of HIF-1alpha in polycythemia, where hypoxic or pseudo-hypoxic conditions activate transcriptional programmes that drive erythropoietin production and erythroid differentiation (Lee *et al.,* 2020; Semenza, 2022). The identification of hematopoietic stem cell differentiation among enriched processes further confirms that the genetic architecture of polycythemia operates at the level of progenitor cell fate decisions, rather than being confined to mature erythrocyte biology alone (Regimbeau *et al.,* 2022).

The GO_Cellular_Component_2023 analysis (Fig. 2) revealed distinct patterns of subcellular localisation, with significant enrichment of genes which encode proteins localised to the nucleus, cytoplasm and extracellular space. Nuclear localisation was particularly prominent for transcription factors and regulatory proteins which are involved in hypoxia response, while cytoplasmic proteins included key enzymes in iron metabolism and oxygen sensing pathways. The presence of extracellular proteins reflected involvement of secreted factors such as erythropoietin and growth factors in the development of polycythemia. The nuclear enrichment of transcription factors governing hypoxia response is directly relevant to the HIF pathway, where HIF-alpha subunits translocate to the nucleus under low oxygen conditions to activate target genes including EPO, VEGFA, and EGLN1 (Semenza, 2022). The presence of extracellular proteins such as erythropoietin and VEGFA in the enrichment is clinically important, as these secreted factors act in

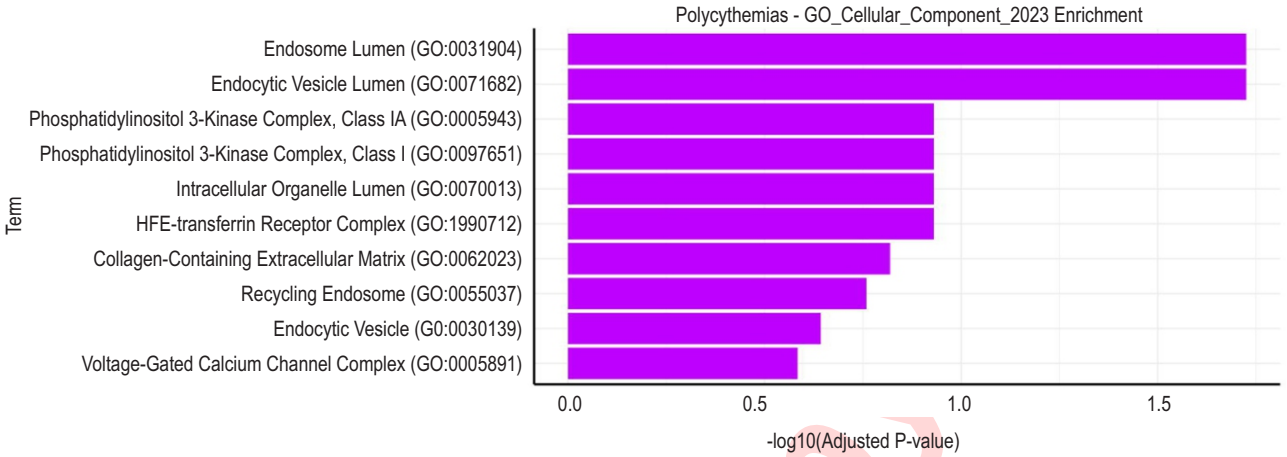

Fig. 2: Cellular Component (CC): Gene Ontology (GO) Cellular Component enrichment analysis of polycythemias. The figure presents cellular components that are most significantly enriched and related to genes associated with polycythemia, this being from 2023 dataset. The x-axis shows the minus log base 10 of the adjusted p-value, while the y-axis indicates the corresponding cellular component terms.

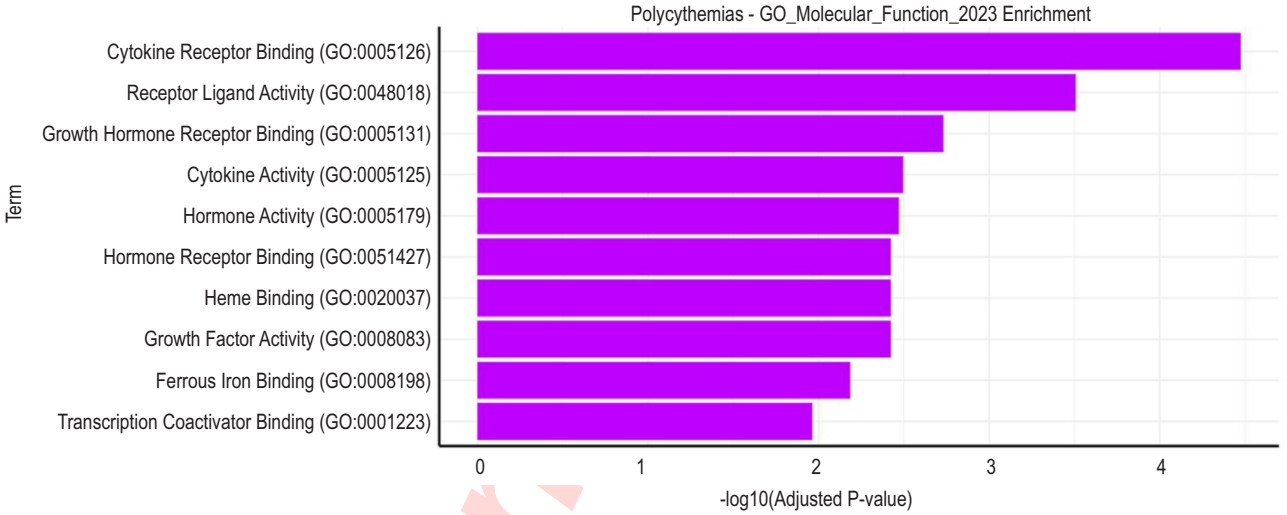

Fig. 3: Gene Ontology (GO) Molecular Function enrichment analysis of polycythemias. The plot highlights the top enriched molecular functions among genes associated with polycythemia, this being from 2023 dataset. The x-axis represents the minus log base 10 of the adjusted p-value, and the y-axis lists the molecular function terms that are significantly enriched.

a paracrine and endocrine manner to amplify erythropoietic drive, and their dysregulation contributes to the phenotypic heterogeneity of polycythemia (Lee *et al.,* 2020).

GO_Molecular_Function_2023 analysis (Fig. 3) identified key molecular activities and these included oxygen binding, iron ion binding, and transcriptional regulatory functions. The enrichment of oxygen and iron binding functions underscore the critical role these molecules play in pathogenesis of polycythemia. Transcriptional regulatory activities were prominently represented, and this reflects the importance of gene expression regulation in maintaining erythropoietic homeostasis. The enrichment of iron ion binding activities aligns with the metabolite findings described later, where iron was significantly associated with TFRC, TMPRSS6, ACO1, and HBA1. Iron availability is a rate-limiting factor in haemoglobin synthesis, and its sensing by these proteins directly modulates erythropoietic output (Camaschella *et al.,* 2020). The transcriptional regulatory functions identified here are consistent with the ChEA findings of hematopoietic transcription factors governing the polycythemia gene network (Semenza, 2022). WikiPathways_2024_14 genes *EGLN1, EDN1, EGLN2, EPAS1, EPO, KLK3, PIK3R1, F2, HIF1A, EPOR, VEGFA, CXCL12, VHL* and *JAK2* were found to be involved in cancer pathways, according to human pathway

Table 1: WikiPathways_2024_Human. The table represents the associated genes, overlap count, p-value, adjusted p-value, and odds ratio, reflecting the strength and statistical significance of each enrichment

Term	Overlap	P. value	Adjusted. P. value	Odds. Ratio	Combined. Score	Genes
Cancer Pathways Wp5434	14/507	p<0.05	0.0000000000007977414	34.56871	1,147.8230	*EGLN1;EDN1;EGLN2;EPAS1; EPO;KLK3; PIK3R1;F2;HIF1A;EPOR; VEGFA; CXCL12; VHL;JAK2*
Type 2 Papillary Renal Cell Carcinoma Wp4241	6/34	p<0.05	0.0000000009169053330	178.05357	4,533.9521	*EGLN1;EGLN2;EPAS1;VHL;HIF1A; VEGFA*
Photodynamic Therapy Induced HIF 1 Survival Signaling Wp3614	5/37	p<0.05	0.0000001577576657302	124.61250	2,481.1222	*EGLN1;EDN1;EPO;HIF1A;VEGFA*
Osteoarthritic Chondrocyte Hypertrophy Wp5373	5/50	p<0.05	0.0000005673792691047	88.55556	1,624.3791	*EPAS1;VHL;JAK2;HIF1A;VEGFA*
JAK STAT Signaling In The Regulation Of Beta Cells Wp5358	4/34	p<0.05	0.0000077621930945832	102.25641	1,585.3747	*GH1;EPO;JAK2;EPOR*

analysis (Table 1), which showed highly significant enrichment of pathways related to cancer with p value less than 0.05, odds ratio equal to 34.57. The strongest enrichment with p value less than 0.05, odds ratio equal to 178.05 was found in the Type 2 Papillary Renal Cell Carcinoma pathway with six genes *EGLN1, EGLN2, EPAS1, VHL, HIF1A* and *VEGFA,* which indicates that polycythemia and some cancers share molecular mechanisms. The co-enrichment of cancer pathways with 14 polycythemia genes is biologically meaningful because it reflects the shared use of hypoxia signaling, angiogenesis, and growth factor pathways between polycythemia vera and malignant conditions. This finding supports clinical observations that polycythemia vera patients carry an elevated risk of transformation to myelofibrosis or acute leukaemia, and it points to common molecular vulnerabilities that could be targeted therapeutically (Regimbeau *et al.,* 2022). The overlap with Type 2 Papillary Renal Cell Carcinoma specifically through *VHL, EGLN1, EGLN2, EPAS1, HIF1A* and *VEGFA* is particularly relevant because VHL loss-of-function mutations are the canonical trigger for constitutive HIF activation in that malignancy, mirroring the pseudo-hypoxic state seen in secondary polycythemia (Shirole and Kaelin, 2023).

The key role that HIF signaling plays in polycythemia was highlighted by the significant enrichment with p value less than 0.05 of the Induced HIF 1 Survival Signaling pathway with 5 genes *EGLN1, EDN1, EPO, HIF1A* and *VEGFA.* Four genes *GH1, EPO, JAK2* and *EPOR* were included in the JAK - STAT Signaling pathway enrichment with p value<0.05, which indicated the pathway's significance in regulation of erythropoietin-mediated erythropoiesis (Table 1). The predominant nuclear and cytoplasmic distribution of proteins associated with polycythemia was revealed by the Jensen_COMPARTMENTS analysis (Fig. 4), which provided a comprehensive information on subcellular localisation. According to this distribution pattern, both transcriptional regulation and cytoplasmic signaling processes are implicated in disease pathophysiology. This nuclear-cytoplasmic distribution is consistent with the known biology of the HIF pathway, where PHD enzymes acting in the cytoplasm hydroxylate HIF-alpha subunits, which then either undergo VHL-mediated proteasomal degradation or translocate to the nucleus to activate target genes (Watts and Walmsley, 2019). The dual compartment involvement, therefore, reflects the two-step regulatory mechanism that controls erythropoietin transcription, and its disruption at either step can drive polycythemic phenotypes (Lee *et al.,* 2020; Semenza, 2022). Tissue-specific expression patterns were shown through Jensen_TISSUES analysis with the highest expression levels found in the liver, kidney and hematopoietic tissues. This distribution supports the physiological relevance of the identified gene set by showing good correlation with the known locations where erythropoietin production and red blood cell formation occur. The enrichment in liver and kidney expression is directly relevant because the liver is the primary site of hepcidin production, which regulates iron availability for erythropoiesis, while the kidney is the dominant site of erythropoietin synthesis in adults (Camaschella *et al.,* 2020). The hematopoietic tissue enrichment confirms that the identified gene set is capturing genuine disease-relevant expression patterns rather than ubiquitous housekeeping genes (Regimbeau *et al.,* 2022).

Key transcription factors which govern genes associated with polycythemia were found through ChEA_2022 analysis, which shed light on the upstream regulatory mechanisms governing gene expression in this disorder. Numerous hematopoietic regulators and hypoxia-responsive transcription factors were identified by the analysis as important regulators of the gene network that was identified. The identification of hypoxia-responsive transcription factors in this analysis is consistent with the GO and WikiPathways findings, where HIF pathway components dominated the enrichment results. Hematopoietic regulators such as GATA1 and other erythroid transcription factors are known to co-operate with HIF signalling to coordinate the erythropoietic response, and their identification

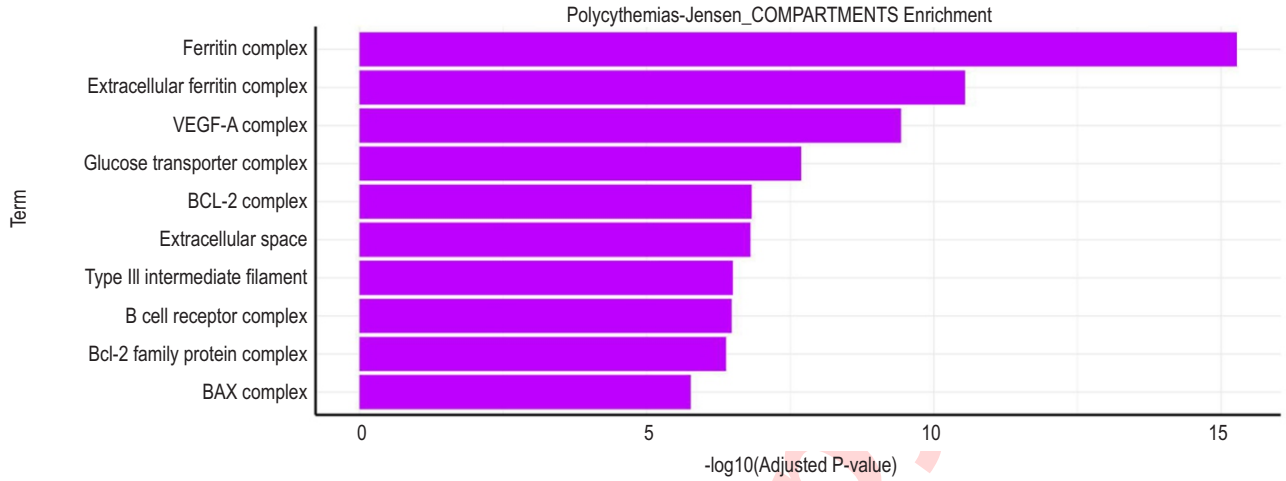

Fig. 4: Jensen COMPARTMENTS enrichment analysis of polycythemias. The bar plot presents the top significantly enriched cellular compartments which are associated with genes related to polycythemia, this being based on the Jensen COMPARTMENTS database from 2023. The x-axis denotes the minus log base 10 of the adjusted p-value, and this indicates the significance of enrichment, while the y-axis lists the corresponding cellular compartments.

here provides an upstream regulatory explanation for the gene expression patterns seen in polycythemia (Gou *et al.,* 2022; Semenza, 2022). Several metabolites were found to be significantly associated with polycythemia genes through HMDB_Metabolites analysis. The strongest correlation between hydroxyproline and the EGLN1 and EGLN2 genes with p value less than 0.05, odds ratio equal to 158.42 demonstrated the function that prolyl hydroxylation plays in HIF regulation.

Four genes TFRC, TMPRSS6, ACO1 and HBA1 were linked to iron with p value <0.05, odds ratio equal to 16.10, which indicated that iron metabolism plays a crucial role in polycythemia. The significance of prolyl hydroxylase cofactors in oxygen sensing mechanisms is further supported by the associations of L-proline and ascorbic acid with EGLN1 and EGLN2. The strong association of hydroxyproline with EGLN1 and EGLN2 is mechanistically significant because these prolyl hydroxylase domain enzymes require L-proline derivatives and ascorbic acid as co-substrates for the hydroxylation of HIF-alpha subunits (Hirota, 2021). When these metabolites are limiting or when the enzymes are mutated, HIF-alpha stabilisation occurs even in normoxia, producing the pseudo-hypoxic drive to erythropoiesis that characterises secondary polycythemia. This direct metabolite-to-gene-to-phenotype connection makes these compounds not just biomarkers but also mechanistic links between nutritional status and polycythemia severity (Watts and Walmsley, 2019). Several pharmaceutical compounds that can alter the expression of polycythemia genes were identified through DrugMatrix analysis. Five genes *EGLN1, CXCL12, TFRC, HIF1A* and *VEGFA* that exhibited the strongest correlation with p value <0.05 with mefenamic acid suggested possible anti-inflammatory effects on pathways linked to polycythemia. On the same gene set, methyl salicylate showed comparable effects with p value <0.05, and suggested similar mechanisms of action. Discovery of metabolic modulators like pioglitazone and rosiglitazone raises the possibility of using metabolic therapies therapeutically for treating polycythemia. The identification of mefenamic acid and methyl salicylate as modulators of the same gene set — *EGLN1, CXCL12, TFRC, HIF1A* and *VEGFA* — suggests that anti-inflammatory inhibition of prostaglandin synthesis pathways may indirectly suppress HIF signalling and erythropoietin production, which is biologically plausible given the known cross-talk between inflammatory mediators and erythropoietic regulation (Caiado *et al.,* 2021). Thiazolidinediones pioglitazone and rosiglitazone, acting through PPAR-gamma, have been shown to modulate mitochondrial oxygen consumption and may, thereby, alter the intracellular oxygen availability that drives HIF activation (Amankwa *et al.,* 2023).

This analysis involving multiple databases provides unprecedented insights into the molecular framework of polycythemia by delineating interconnected regulatory networks which govern cellular metabolism, oxygen sensing, and erythropoiesis. The findings not only enhance understanding of disease mechanisms but also highlight potential therapeutic targets that could be exploited for clinical interventions. The enrichment of hypoxia-inducible factor abbreviated as HIF signaling pathways underscores the pivotal role that oxygen-sensing mechanisms play in disease development. Several HIF components, these including EGLN1, EGLN2, EPAS1, HIF1A and VHL, were identified as central players, and this is consistent with prior evidence that dysregulation of oxygen sensing is a fundamental pathogenic mechanism (Semenza, 2022). The strong association of VHL mutations with constitutive HIF activation and secondary polycythemia in conditions such as Type 2 Papillary Renal Cell Carcinoma (Shirole and Kaelin, 2023)

reinforces the shared molecular pathways between polycythemia and certain malignancies, and this potentially explains the increased cancer risk in affected patients.

Metabolite associations further support the mechanistic basis of HIF regulation. Hydroxyproline, L-proline, and ascorbic acid, are the cofactors and substrates for prolyl hydroxylase enzymes that strongly correlate with polycythemia genes. These metabolites are critical for the hydroxylation of HIF-α subunits in normoxic states, and this targets them for VHL-mediated degradation (Hirota, 2021). Altered prolyl hydroxylase activity, leading to impaired metabolite utilisation, may stabilise HIF inappropriately, thereby enhancing erythropoietin production (Watts and Walmsley, 2019). The enrichment of erythropoietin signaling and JAK-STAT components such as EPO, EPOR and JAK2 validates their central role in pathophysiology of polycythemia. The frequent occurrence of JAK2 mutations in polycythemia vera and their role in constitutive pathway activation (Gou *et al.,* 2022) aligns with these results. Identification of GH1 within the JAK-STAT network also points to potential interactions between erythropoiesis and growth hormone signaling, and this offers a possible explanation for phenotypic variability in certain patients (Hu *et al.,* 2021).

Iron metabolism emerged as another critical determinant, with strong correlations between metabolites related to iron and genes such as TFRC, TMPRSS6, ACO1 and HBA1. Iron availability directly affects erythropoiesis, and disturbances in iron sensing or hepcidin regulation, particularly through TMPRSS6, may contribute to disease progression (Camaschella *et al.,* 2020). These findings are clinically significant given that iron restriction has been considered as a therapeutic strategy in selected polycythemia cases. DrugMatrix analysis identified compounds which include methyl salicylate, mefenamic acid, rosiglitazone, and pioglitazone as modulators of polycythemia gene expression. Anti-inflammatory agents point to inflammation as a possible contributor to disease mechanisms, particularly through its influence on erythropoietin regulation or hematopoietic stem cell function (Caiado *et al.,* 2021). Similarly, metabolic modulators which affect mitochondrial function and oxygen consumption (Amankwa *et al.,* 2023) highlight additional therapeutic opportunities.

Tissue-specific expression analysis revealed the liver, kidney and hematopoietic organs as primary sites where polycythemia gene expression occurs, and this is in line with the physiology of erythropoietin production. Subcellular localisation patterns spanning nuclear and cytoplasmic compartments suggest regulation occurring at both transcriptional and post-transcriptional levels.Together, these findings reveal that polycythemia is underpinned by diverse molecular mechanisms, with different patients potentially being driven by HIF dysregulation, JAK-STAT activation, or abnormalities in iron metabolism. This heterogeneity underscores the importance of individualised therapeutic approaches which are tailored to the underlying molecular drivers in each patient.

This study, while providing valuable exploratory insights through bioinformatics analyses, is subject to certain limitations. The findings are primarily based on available datasets, and these may have inherent biases or inconsistencies in data quality and completeness. Additionally, variations between databases and differences in data annotation standards may have influenced some of the outcomes. As this work is exploratory in nature, the results should be interpreted with caution and viewed as a foundation for further validation and experimental confirmation. Future studies incorporating larger datasets that are more diverse and complementary laboratory approaches would help to strengthen and refine the conclusions which have been drawn from these analyses.

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