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Phenotypic variability in von Hippel-Lindau disease, efficacy of therapy, and prognosis. A review of the literature

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ABSTRACT

Von Hippel-Lindau disease is an inherited cancer predisposition that occurs due to an incorrect structure or a lack of the von Hippel-Lindau protein. Von Hippel-Lindau disease is known to have a noteworthy phenotypic variability and an elevated risk of developing tumors. A multitude of publications have demonstrated the correlation of the severity of a disease with a patient's genotype. Missense mutations in exon three are associated with one of the most severe outcomes, including the elevated risk of clear cell renal cell carcinoma and pancreatic neuroendocrine tumors. Deletions in exon one significantly raise the risk of developing pheochromocytomas. The review proved the importance of tailoring the therapeutic strategy to the genetic profile of the patient. Belzutifan shows high efficacy in treating patients with mutations in exon three. The development of gene therapy, which is currently in preclinical testing, could become a groundbreaking approach to treatment. Heterogeneity of VHL gene mutations leads to high phenotypic variability in the disease. It directly modulates the disease course, treatment efficacy, and prognosis. Early molecular diagnostics and personalized therapy based on the genetic profile are critical for improving patient care. Further studies and the improvement of modern therapeutic approaches, including gene therapy, are necessary.

Keywords: VHL, Hif pathway, hypoxia, genotype-phenotype correlation, treatment

1. INTRODUCTION

Von Hippel-Lindau disease (VHL disease) (OMIM: 193300) is a genetic disorder inherited in an autosomal dominant manner. It leads to an increased genetic predisposition to tumors. The condition arises from various mutations in the VHL gene. Mutations in the VHL gene are known to increase the probability of developing tumors like pancreatic neuroendocrine tumors (PNETs), pheochromocytomas, clear cell renal cell carcinoma (ccRCC), and both retinal and central nervous system (CNS) hemangioblastomas (Maher et al., 2011). According to estimates, the disease affects one in thirty-six thousand people. According to estimates, one in thirty-six thousand people suffer from this disease. In Poland,

approximately one thousand one hundred patients live with VHL disease (Lubiński, 2022).

The symptoms and the onset age within patients with VHL mutations are highly variable due to the nature of the disease. The average age of diagnosis is twenty-three years. An average life expectancy without treatment is around fifty-nine years for men and around forty-eight years for women (Lubiński, 2022). The significant phenotypic variability depends mainly on the type and location of the mutation. Twenty percent of all VHL gene mutations arise de novo and lack a family history.

Estimates say that VHL may be responsible for (Maher et al., 2011): About one-third of CNS hemangioblastoma cases, Over fifty percent of retinal hemangioblastoma cases, One percent of renal cell carcinoma cases, Fifty percent of isolated familial pheochromocytomas, Eleven percent of apparently sporadic pheochromocytomas.

Tumors develop multifocally, bilaterally, and at a young age, with treatment primarily relying on surgical and pharmacological methods. The Polish VHL registry, based in Szczecin, has been functioning since 1997 at the International Hereditary Cancer Center in Szczecin.

The purpose of this work is to describe how the genotype of a patient determines the manifestations of VHL disease. The article focuses on the treatment efficacy and prognosis for the patient, which is defined based on a review of the present literature. Understanding the above interactions is essential for adjusting the diagnostic and treatment process, which can improve the quality of life of patients.

Molecular basis of VHL disease

The VHL gene is approximately ten thousand base pairs in length. It consists of three exons and encodes the von Hippel-Lindau protein (VHLp), which is also called the von Hippel-Lindau tumor suppressor. VHLp has a significant role in cellular adaptation to hypoxia because it regulates the stability of hypoxia-inducible factor (Hif) proteins.

Hif proteins include Hif1α, which has two isoforms (Hif2α and Hif3α), and Hif1β. The stability of Hif1α proteins depends on the partial oxygen concentration, Hif1β is constitutively stable, and Hif3α inhibits the binding of Hif1α to DNA (Wojcierowski, 2022).

In normoxic conditions, Hifα proteins (Hif1α and Hif2α) undergo hydroxylation by the Egln hydroxylase (prolyl hydroxylase), enabling binding to VHLp. The VHLp/Hifα complex is then directed to the apoptosis pathway via E3 ubiquitin ligase. In hypoxic conditions, VHLp cannot form a complex with Hifα, leading to an inability to degrade Hifα. The accumulation of Hifα causes it to bind with Arnt/Hif1β. The established complex translocates to the nucleus, where it initiates the transcription (Wojcierowski, 2022). Figure 1 summarizes the primary mechanism of Hif1α regulation.

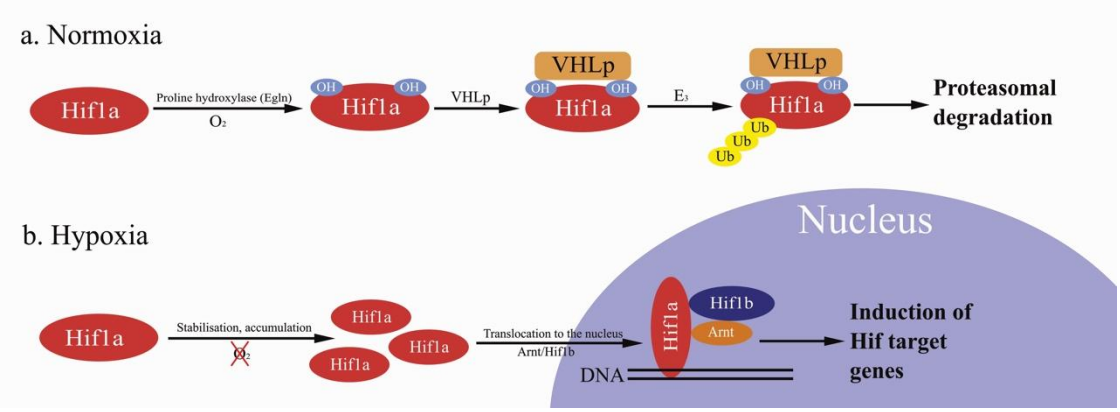

Figure 1: In normoxia, Hif1α undergoes proteasomal degradation. (b) In hypoxia, Hif1α stabilization and accumulation occur, leading to its translocation into the nucleus and inducing angiogenesis.

The action of Hif1α, similar to that of Hif2α, causes the expression of erythropoiesis, angiogenesis, genes encoding vasodilator proteins, and other genes. Also, Hif1α inhibits cell division by halting Myc protein function and activating the expression of cyclin-dependent kinase (CDK) inhibitors. Unlike Hif1α, Hif2α stimulates the course of the cell cycle by increasing the reciprocal interaction of Myc and Max proteins and activating Myc target genes. Activation of both complexes results in increased production of fibroblast growth factor 1 (Fgf1) and cyclin D1 (Wojcierowski, 2022).

Roe et al., (2006) showed that the VHLp directly interacts with p53, and leads to stabilization of its function. In HEK293 cells, coimmunoprecipitation allowed them to confirm the formation of the VHLp/p53 complex. The observed results suggest that VHLp stabilizes p53, affecting its activity regardless of other proteins. The presence of mutations in the VHL gene results in a malfunctioning VHLp structure. It can become completely non-functional, or it can have a limited function, depending on the mutation type and location.

When the VHLp is impaired, it results in overexpression of proangiogenic genes, which promote carcinogenesis. The phenotypic variability in VHL disease stems from the mutation heterogeneity. This principle affects the type, location, and age of tumor manifestation. Understanding the molecular role of VHLp and genotype-phenotype correlations allows clinicians to personalize patients' diagnosis and therapy, making it possible for them to improve treatment strategies and predict the progression of the disease.

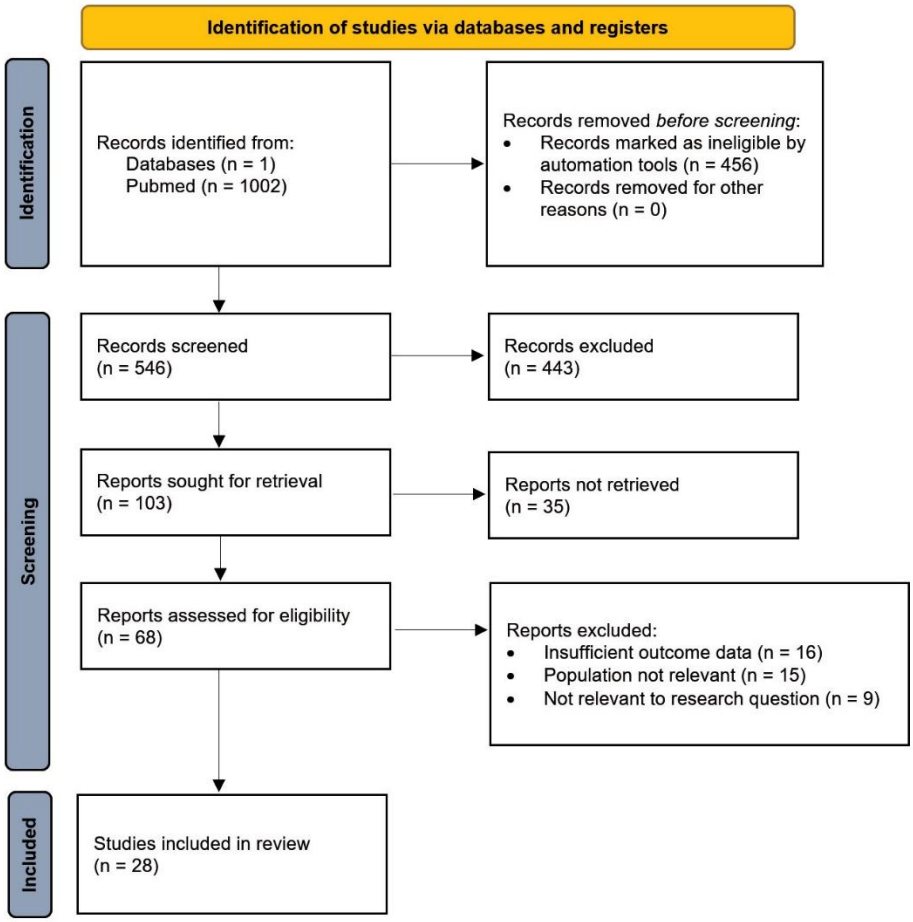

Figure 2: PRISMA flow diagram.

2. REVIEW METHODS

To achieve the stated aim of this study, a systematic literature review was conducted using the PubMed database, based on articles on genotype-phenotype correlation in VHL disease. Original research articles, systematic reviews, and meta-analyses that covered phenotypic variation, treatment efficacy, and prognosis in patients suffering from VHL disease served for the analysis.

Keywords selected based on their relevance to examining the matter in the subject, such as VHL, von Hippel-Lindau, phenotypic variability, genotype-phenotype, correlation, and therapy, were used in the process of article selection. Keywords were applied in various combinations with logical operators (AND, OR). Studies were selected based on their relevance to the subject. The first step in the selection of the literature needed for review consisted of reviewing the titles and abstracts. The chosen articles, then, were screened based on the full text by two independent researchers. Disagreements in evaluations were resolved through consensus to ensure the high quality and reliability of the selected sources. The analysis incorporated information from textbook literature on molecular biology

and clinical genetics, including monographs. These works laid the foundation for understanding the molecular mechanisms of VHL disease. The article screening process adhered to the PRISMA guidelines (Figure 2).

Exclusion criteria:

- Articles not related to VHL disease,
- Studies without an explicit reference to genotype-phenotype correlation or treatment outcomes.

3. RESULTS & DISCUSSION

A review of the literature reveals that specific VHL gene mutations are particularly characteristic of certain clinical phenotypes. Missense mutations in exon three result in a notably increased risk of PNETs within patients suffering from VHL disease. It is a finding that was supported by Blansfield et al. and later genotypic and clinical analyses (Blansfield et al., 2007; Tirosh et al., 2018; Xu et al., 2024; He et al., 2023; Binderup et al., 2016). This observation is clinically reflected in a structured risk prediction model, which incorporates the presence of exon three mutations as a criterion showing a high likelihood of metastasis (Blansfield et al., 2007).

Data from the Chinese population add further layers to this profile, showing that missense mutations not only increase PNET risk but also reduce the incidence of CNS hemangioblastomas and pancreatic cystic lesions (Peng et al., 2017). In the same context, large deletions within the VHL gene are strongly correlated with a bigger risk of retinal hemangiomas, which are some of the earliest diagnosed and most often reported ocular manifestations (Peng et al., 2017; Wittström et al., 2014; Karimi et al., 2020).

Cohort analyses from both Western and Chinese populations have proven that truncating mutations confer a substantially higher ccRCC risk compared to missense variants (Ruppert et al., 2019; Binderup et al., 2013; Gossage et al., 2015). Additionally, studies suggest that mutations resulting in impairment of Jade-1 protein stabilization correlate with a severe ccRCC course (Zhou et al., 2004).

Attention is also drawn to studies writing down that frameshift mutations in exon one do statistically significantly enlarge the probability of developing pheochromocytoma in younger patients (Nordstrom-O'Brien et al., 2010; Rednam et al., 2017). In patients who have missense mutations within the elongin C-binding domain, there is similarly an increased risk of developing pheochromocytoma, though without hemangioblastoma. Numerous family studies and meta-analyses confirm the previously mentioned fact (Maher et al., 2011; Binderup et al., 2013; Nordstrom-O'Brien et al., 2010; Nielsen et al., 2011; Huang et al., 2018).

An abundance of histopathologic examinations performed on divergent cohorts of individuals reveals that the most frequent ocular manifestations within VHL disease-positive patients are caused by the loss of heterozygosity (LOH) type mutations (Maher et al., 2011; Blansfield et al., 2007; Peng et al., 2017; Wittström et al., 2014; Karimi et al., 2020; Rednam et al., 2017; Wiley et al., 2019). The findings included vascular retinopathies, along with retinal hemangiomas, as the most frequent ocular manifestations. Also, observations show that up to sixty percent of patients develop ocular manifestations before the age of thirty (Karimi et al., 2020).

Moreover, epigenetic studies as well as somatic mutation analyses of the VHL gene in renal tumors have revealed that loss of its function, due to LOH type mutation, promoter methylation, or truncation mutations, represents a consistent feature in the pathogenesis of ccRCC, in both hereditary and sporadic forms (Banks et al., 2006; van Houwelingen et al., 2005). The emerging studies using radiogenomics suggest that it may become possible to predict the VHL mutation profile based on the imaging characteristics of ccRCC (He et al., 2023). This finding can potentially open up opportunities for noninvasive monitoring in mutation carriers. In the era of personalized medicine, this approach could show the benefits of a precisely tailored care regimen compared to generalized guidelines. Table 1 describes selected severe mutations in the VHL gene.

Table 1: Severe mutations in the VHL gene – localization, phenotypic expression, and clinical relevance.

Location	Type	Common Clinical Phenotype	Selected Clinical Features
Exon 1	Frameshift	Pheochromocytoma	Frequent in young patients
Exon 3	Missense	PNETs, ccRCC	Increased metastasis risk; aggressive course
Exon 3	Truncating (nonsense, splicing)	ccRCC	High risk of bilateral ccRCC
Exon 1 / multiexon	Large deletions	Retinal hemangiomas, retinopathies	Occurs earlier (<30 y.o.); may lead to blindness
Various (heterogeneous)	LOH, promoter methylation	ccRCC (hereditary and sporadic)	Loss of VHL gene function, epigenetic features

A review of the literature shows that the phenotypic variability in VHL disease is closely related to the type and location of the mutation present in the VHL gene. This correlation has a direct impact on the choice of a proper therapeutic strategy and prognosis. Exon three mutations are known for a more severe course compared to exons two and one. Patients with exon three mutations characteristically have a higher risk of developing ccRCC, with lesions occurring multifocally (Blansfield et al., 2007; Ganner et al., 2025). When compared to exon three, mutations in exon one result in a milder course, with features such as pheochromocytomas, which require a completely different diagnostic and therapeutic approach (Peng et al., 2017; Ganner et al., 2025). The data findings are in agreement with earlier studies pointing to the value of mutation heterogeneity in the course of VHL. Table 2 shows selected therapeutic methods used in VHL therapy and their areas of application.

Table 2: Therapeutic methods and their applications in VHL

Therapeutic Method	Indications	Efficacy	Limitations	Remarks
Belzutifan	ccRCC, PNETs	49% for ccRCC; 63% for CHB; 83% for PNET (LITESPARK-004)	No randomized clinical trials (RCTs); side effects: anemia (93%), fatigue, hypoxia (1.6%)	First approved systemic therapy (FDA, 2021); of particular interest in patients with exon 3 mutations
Active surveillance	Small, benign tumors	Variable; minimizes recurrence	Requires a strict observation schedule	Standard in tumors with low risk of progression
Interventional Surgery	ccRCC, CHB, pNET, pheochromocytomas requiring immediate resection	Partial nephrectomy effective	Frequent necessity for multiple treatments; high risk	Standard method in advanced tumors; specific to location and phenotype
Radiotherapy (stereotactic)	CHB in hard-to-reach locations; when surgery is contraindicated	Effective for CHB	Limited long-term efficacy data; risk of cerebral edema.	Used less frequently, mainly in specific cases of CHB.
VEGF/mTOR Inhibitors (e.g. sunitinib, everolimus)	Advanced ccRCC (experimental)	Limited efficacy in VHL; studied in ccRCC	High risk of side effects; no FDA approval in VHL	Used off-label or in clinical trials; less effective than belzutifan.
Immunotherapy (e.g. nivolumab)	Advanced ccRCC (experimental)	Being studied in sporadic ccRCC; limited data for VHL	No approval for VHL; side effects	Experimental, needs further research in VHL
Gene Therapy	Potentially all VHL-related tumors (preclinical phase)	Promising results in preclinical models; no clinical data available	Lack of approval; Challenges: mutation heterogeneity, vector delivery, off-gene effects	Experimental; possible future option, especially for mutations in exon 3

The Food and Drug Administration (FDA) in August 2021 approved belzutifan, an oral Hif2α inhibitor, as the first systemic therapy for adult patients requiring treatment for cancers such as ccRCC, CNS hemangiomas, or VHL-associated PNETs (FDA, 2022). Due to the lack of randomized controlled trials (RCTs), available information about the effectiveness of belzutifan is still inconclusive. The LITESPARK-004 study was an open-label trial without a control group, limiting the ability to compare it with other treatment methods such as active surveillance or surgery (Srinivasan et al., 2025).

With a better understanding of molecular mechanisms in the VHL disease, promising treatment strategies, such as gene therapy, appear. Trends in research are mainly focused on the development of technologies to restore the physiological functions of the VHL gene or to compensate for mutations via modulation of the Hif pathway. The use of viral vectors such as adeno-associated virus (AAV) or lentivirus to introduce correct sequences into the VHL gene in somatic cells is also under consideration. The CRISPR/Cas9 genome editing method is frequently described in publications in its preclinical state as being highly promising as well. Numerous studies suggest that once gene therapy is developed, it is possible that it will be used along with adjunctive drugs such as the exemplary belzutifan.

Heterogeneous data in the literature limit the review due to differences resulting from differences in study methodology, cohort size, and phenotype reporting. There is no standardization in describing genotype-phenotype correlations in VHL disease, which also makes the research process harder. Further prospective research is needed for a better comprehension of the impact of specific mutations on treatment response and prognosis.

4. CONCLUSION

The variability of manifestations in a course of VHL disease results from the wide range of mutations in the VHL gene and significantly affects both the therapeutic efficacy and prognosis for the patient. Mutations in exon three of the VHL gene are associated with a more severe phenotype in comparison to mutations of exons one and two. These patients need, thus, more vigilant surveillance and personalized treatment strategies. Early molecular diagnostics and regular imaging studies can positively affect the patient's fate and quality of life. Systematic imaging studies adjusted to the individual's risk of developing genotype-specific tumors are recommended.

Belzutifan, as the first Hif2α inhibitor approved for VHL therapy, may open the next era of therapeutic approaches in VHL. Despite promising therapeutic effects so far, randomized trials are necessary to confirm its efficacy. Radiotherapy and targeted therapies such as VEGF inhibitors, mammalian target of rapamycin (mTOR) kinase inhibitors, or immunotherapy with appropriate use are considered good adjunctive or experimental methods. However, they have limited efficacy, and their use is not officially registered for VHL therapy. Further research is needed to enhance and personalize treatment for VHL disease.

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Author's contribution

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Informed consent

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Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

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Conflict of interest

The authors declare that they have no conflicts of interests, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on reasonable request to the Corresponding Author.

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