Aetiological Risk Factors for Congenital Haemangiomas in Children

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Abstract: *Background*: Congenital haemangiomas are rare vascular tumours in children, and their complex aetiology involving genetic, hormonal, and environmental factors remains insufficiently understood.

Purpose: This study aims to systematise and analyse data on the aetiological risk factors for congenital haemangiomas in children. The main objective was to identify key trends and patterns related to the aetiology of the disease.

Methods: A structured review of 46 published sources (2013-2025) was conducted, including peer-reviewed articles, clinical case reports, and molecular studies. 91% of the included sources were published within the last 5-6 years. Materials were examined using thematic analysis, comparative methods, and systematic organisation, integrating both quantitative and qualitative approaches to assess genetic, hormonal, environmental, and perinatal risk determinants.

Findings: Genetic mutations, such as missense mosaic mutations in *GNAQ* and *GNA11*, as well as the pathogenic somatic variant *PIK3CA* (p.His1047Gln) with an allele frequency of 8.3%, play a key role in the pathogenesis of congenital haemangiomas. Mutations in the *VEGF-A* and *TIE2* genes also contribute to their development. Newborns with large placental chorioangiomas are more likely to develop haemangiomas. Oestrogens stimulate the proliferation of vascular cells; approximately 60% of children with periorbital haemangiomas are girls, which indicates the role of female sex hormones in the pathogenesis of haemangiomas, and hypoxia affects the expression of angiogenic inducer 61. Klippel-Trénaunay syndrome can cause haemangiomas, especially when internal organs are affected. Data showed that infantile haemangiomas occur in 75% of children with a gestational age of less than 33 weeks and in 57% of children with a gestational age of 33 to 37 weeks. Hyperemesis gravidarum can cause deficiencies of essential micronutrients in the mother, increasing the risk of congenital haemangioma by 1.75 times. The use of medications during pregnancy also increases the risk of developing a congenital hemangioma by 1.8 times

Conclusion: The results of the study can be used to develop new approaches to the diagnosis and treatment of congenital hemangiomas in children, as well as to create more accurate and personalised treatment methods that account for genetic and environmental risk factors.

Keywords: Genetic mutations, infantile haemangiomas, angiogenesis, hypoxia, oestrogens, prematurity, environmental factors.

INTRODUCTION

Congenital haemangiomas (CH) are fully formed benign vascular tumours present at birth, with an estimated incidence of 0.3%, compared with the broader category of haemangiomas, which occur in 4-10% of infants [1-3]. Clinically, CH typically appear as painless, well-circumscribed vascular plaques or masses – dark purple or bright red with a pale halo – that protrude slightly from the skin surface [4]. Despite their rarity, CH require careful diagnostic evaluation, and understanding their aetiological determinants is essential for improving management strategies.

While existing research has elucidated several genetic mechanisms underlying CH, much less is known about the contribution of molecular, epigenetic, hormonal, environmental, and hypoxic influences. This gap highlights the need for an integrated examination of diverse risk factors to advance the understanding of CH pathogenesis.

Epidemiological observations indicate that haemangiomas most commonly occur on the face. Alymbaev *et al*. [5] reported facial localisation in 73% of 22 examined children, and Omurzakov [6] found similar patterns in 84% of 52 cases, underscoring the anatomical region's vulnerability. Genetic studies further reveal mosaic mutations in the *GNAQ* and *GNA11* genes – specifically substitutions at amino acid position 209 – across multiple CH subtypes, including visceral lesions, suggesting disrupted G-protein signalling as a central pathogenic mechanism [7].

Histopathological research has demonstrated structural evolution in childhood haemangiomas, with early capillary patterns often transitioning into cavernous architecture over time [8]. Broader risk factor analyses, such as that by Melgosa Ramos *et al*. [9], additionally associate congenital and infantile haemangiomas with prematurity, low birth weight, IVF conception, extended gestational age, and maternal

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pre-eclampsia. The clinical burden of CH can be significant, as shown by Braun *et al*. [10], who documented complications including foetal heart failure, neonatal thrombocytopenia, ulceration, and, in rare cases, severe haemorrhage. Diagnostic challenges persist: Safin *et al*. [11] emphasised that inadequate early imaging, particularly the absence of Doppler ultrasound, may lead to misclassification and suboptimal treatment.

The study aims to address the following issues: identifying key aetiological factors associated with congenital haemangiomas and analysing genetic mutations that influence their development.

This study conducted a comprehensive analysis of the aetiological risk factors for congenital haemangiomas in children. This includes analyses of genetic, epigenetic, environmental, hormonal, and family history factors. Thus, this study aims to comprehensively examine the aetiological risk factors, enabling a more complete understanding of the causes of congenital haemangiomas and the development of effective treatment methods.

MATERIALS AND METHODS

This study was based on a review of published sources on the aetiological risk factors for congenital haemangiomas in children. This approach enables systematising and analysing existing knowledge, as well as identifying key trends and patterns in this field. The review includes an analysis of scientific articles, studies, books, clinical cases, and other publications that contain data on the causes, mechanisms, and risk factors for the development of congenital hemangiomas.

The study covers publications from 2013 to 2025, ensuring the inclusion of the latest data and trends in this field. The time frame was chosen to balance fundamental research with cutting-edge discoveries, with 91% of sources no older than 5-6 years.

The literature reviewed includes peer-reviewed articles from scientific journals and books, as well as contributions from well-known research groups. The search and analysis of sources was conducted using authoritative platforms such as PubMed, PMC, ResearchGate, MDPI, Gazi Medical Journal, Lippincott Williams & Wilkins Journals, Actas Dermo-Sifiliográficas, IntechOpen, and Fortune Journals.

Keywords and keyword combinations were used to search for literature, such as "congenital haemangiomas," "aetiology of haemangiomas," "risk factors for haemangiomas," "genetic aspects of haemangiomas," "environmental factors of haemangiomas," and "clinical cases of haemangiomas." These keywords covered a wide range of publications related to the research topic.

The relevance of publications was determined by analyzing the abstracts, introductions, and conclusions of the articles. The primary focus was on studies that presented new data, hypotheses, or methodologies related to the aetiology of congenital haemangiomas. The selection criteria included the novelty of the data, methodological rigour, and relevance of studies directly related to the aetiology of congenital haemangiomas. Sources were excluded if they were not relevant to the topic under consideration, contained repetitive information, did not provide sufficient detail for adequate assessment, or if their results did not apply to the study.

In total, 87 records were identified, of which 81 remained after duplicates were removed. All records were screened, and 46 full-text articles were retained for the final synthesis. Potential bias was mitigated through the use of predefined inclusion and exclusion criteria, dual independent screening of titles and abstracts, and consensus-based resolution of discrepancies. Duplicate data were minimised by systematically cross-checking studies for overlapping cohorts and by excluding publications that presented the same dataset in different formats. Figure **1** illustrates the process of selecting sources for the systematic review of studies.

The collected materials were analysed using thematic analysis, comparative methods, and systematic organisation. Thematic analysis included classifying sources according to key themes such as genetic factors, environmental influences, clinical manifestations, hypotheses about mechanisms of development, and statistical data. Comparative analysis revealed common and unique aspects across sources, helping determine which conclusions were supported by multiple studies and which required further verification.

Both quantitative and qualitative approaches were used to analyse the data. Quantitative analysis included counting the frequency of mentions of specific risk factors and statistical analysis of the data. Qualitative analysis focused on interpreting the hypotheses and conclusions presented in the studies.

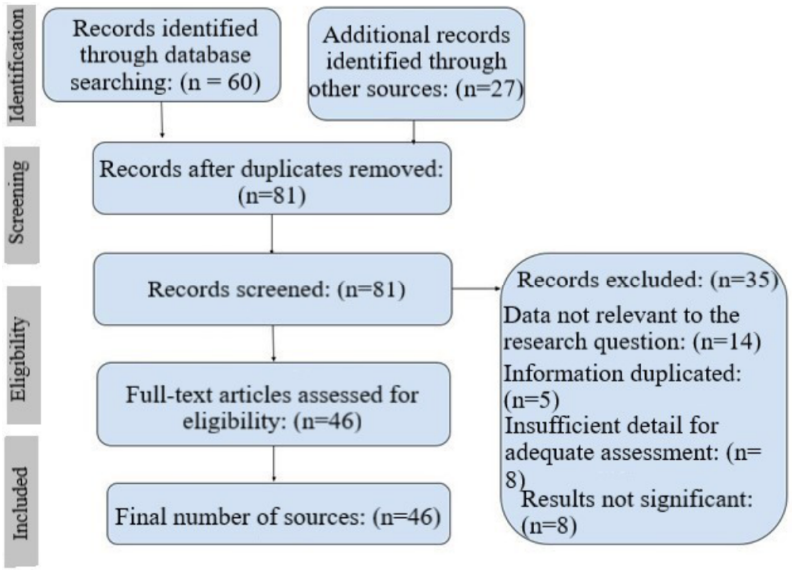

Figure 1: Process of selecting sources for a systematic review of studies on the aetiological risk factors for congenital haemangiomas in children.

Note: the PRISMA diagram shows the stages of source selection, from identification to inclusion in the review. Each stage includes an indication of the number of sources and the exclusion criteria, ensuring transparency and repeatability of the selection process.

Source: compiled by the authors.

A comparative analysis was conducted to identify common and unique aspects across different sources. This approach helped to determine which conclusions were supported by multiple studies and which required further verification.

The methodology and conclusions of each study were critically evaluated to assess their reliability and relevance. The critical evaluation included a review of the method, analysis of the results, and assessment of the significance of the conclusions for understanding the aetiology of congenital haemangiomas. Specific evaluation parameters included sample size, data quality, analytical approaches, and the presence of control groups. Sources that met high methodological rigour standards and yielded meaningful results were considered the most authoritative. Sources with insufficient sample sizes or ambiguous results required additional evidence.

All materials from published sources were used in strict accordance with copyright ethics. References and data were correctly attributed to their sources and authors, ensuring the ethical use of scientific data and respect for the work of researchers.

RESULTS AND DISCUSSION

Congenital haemangiomas (CH) are benign vascular tumours that reach their maximum size by the time of birth and do not show accelerated postnatal growth. These tumours can be classified into three subgroups: rapidly involuting congenital haemangioma (RICH), non-involuting congenital haemangioma (NICH), and partially involuting congenital haemangioma (PICH). RICH is characterised by rapid regression within the first few months of life, while NICH maintains its size and structure throughout the patient's life. PICH demonstrates partial regression but does not entirely disappear [12].

The aetiology of haemangiomas is a dynamic process that begins with the rapid proliferation of blood vessels through angiogenesis, followed by a slow involution phase in which the lesion regresses and is replaced by fibro-fatty tissue [13].

Haemangiomas, or infantile haemangiomas (IH), are the most common benign tumours in infants. They are often called "strawberry marks" due to their characteristic appearance. These formations arise from excessive endothelial cell proliferation. There are several types of haemangiomas: congenital, which are visible immediately at birth, and infantile, which appear later. Infantile haemangiomas are characterised by rapid growth in the early stages, followed by spontaneous regression [14].

IH and CH are vascular tumours of infancy, but they differ in their primary causes and clinical course. In the

Table 1: Differences between Congenital Hemangioma and Infantile Hemangioma

Characteristics	Congenital hemangioma	Infantile hemangioma
Presence at birth	Present	Visible between 2 weeks and 4 months of age
Growth	Complete at birth or proportional to the child's growth	Rapid growth within 6-12 months
Sex ratio	Male: Female = 1:1	Male: Female = 1:3-5
Prevalence	Less common, but not rare	Common (4-5% of newborns)
Involution	Rapid or non-existent	Slow regression
GLUT-1	Negative	Positive
Proliferation phase	Large and irregularly shaped vessels	Small regular capillaries

Source: compiled by the authors based on [17].

case of IH, it is believed that the lesions result from dysregulation of vasculogenesis and angiogenesis. Hypoxic stress appears to act as a trigger, leading to the overexpression of vascular endothelial growth factor (VEGF) and other angiogenic factors, which in turn drives the abnormal proliferation of foetal endothelial cells. This process explains the rapid growth of IH in the first weeks and months of life, followed by gradual involution. In the case of CH, somatic activating mutations play a key role in its pathogenesis [15, 16]. These differences underscore the need to differentiate between these types of haemangiomas to ensure accurate diagnosis, as clearly illustrated in Table **1**.

A non-involuting congenital haemangioma, despite its definition as a tumour that does not involute and persists throughout life, can show proportional growth and changes over time. This phenomenon may be due to the presence of high-flow vessels in the NICH structure, which contributes to the late development of the tumour [18].

Studies have described several cases of NICH demonstrating postnatal growth and changes. In a six-week-old girl, a congenital vascular lesion on her shoulder showed proportional growth and the development of telangiectasias by age 2. In a four-week-old boy, a light blue lesion in the retroauricular area increased in size and became darker after two months. In a 14-year-old girl, a flat lesion on her scalp developed into an exophytic tumour that required surgical removal. These observations highlight that NICH can show significant changes and growth in both early childhood and adolescence [19].

Genetic mutations associated with congenital haemangiomas include mosaic missense mutations in the GNAQ and GNA11 genes. These mutations change glutamine at amino acid 209 (Glu 209) and have been found in tissue samples from patients with congenital haemangiomas. Mutations in the GNAQ and GNA11 genes can affect the activity of G-proteins, which play an essential role in cell signalling. These changes can contribute to abnormal endothelial cell growth, leading to the formation of haemangiomas. Six out of eight samples were associated with somatic mutations in the GNAQ gene, and two out of eight were associated with a mutation in the GNA11 gene. The same mutation was found in both RICH and NICH. This

Table 2: Mutations in the GNAQ and GNA11 Genes Associated with Congenital Hemangiomas

Gene	Mutation in CDS (coding DNA sequence)	Mutation in AA (amino acid mutation)
GNAQ	c.626A>T	p.Gln209Leu
	c.625_626delinsTT	p.Gln209Leu
	c.627A>C	p.Gln209His
	c.626A>C	p.Gln209Pro
GNA11	c.626A>T	p.Gln209Leu
	c.626_627delinsTA	p.Gln209Leu
	c.626_627delinsTT	p.Gln209Leu

Source: compiled by the authors based on [21].

indicates that mutations in these genes can play a key role in the development of haemangiomas but do not determine their clinical behaviour, such as the rate of involution [20]. Table **2** presents specific mutations in the DNA coding sequence and the corresponding amino acid changes associated with this condition.

Based on the data presented in Table **2**, all identified mutations in *GNAQ* and *GNA11* affect the same amino acid residue, glutamine at position 209 (Gln209), indicating the critical role of this position in the pathogenesis of congenital haemangiomas. Regardless of the type of substitution (to leucine, histidine, or proline), the Gln209 change disrupts the normal function of G-proteins, which can contribute to the proliferation of endothelial cells [21].

Pilch *et al.* [21] agree that congenital haemangiomas are associated with genetic mutations that affect cell signalling. Both studies emphasise the role of mutations in the *GNAQ* and *GNA11* genes, which result in an amino acid change at Glu 209 and affect G-protein activity, contributing to abnormal endothelial cell growth. Yeh *et al.* [22] identified *GNAQ* mutations in one solitary pulmonary capillary haemangioma and one pulmonary cavernous haemangioma, confirming that *GNAQ* mutations can be found not only in cutaneous haemangiomas but also in other locations. This data confirms that mutations in genes that regulate cell signalling can play a key role in the development of congenital haemangiomas and are an essential aetiological factor in their formation.

In addition, congenital haemangiomas have been linked to an activating pathogenic *PIK3CA* variant. Genetic sequencing found a pathogenic somatic *PIK3CA* variant (p.His1047Gln) with an allele frequency of 8.3%. This gene encodes a subunit of phosphatidylinositol-3-kinase (*PI3K*), a key regulator of cell growth and proliferation. Mutations in PIK3CA can activate the *PI3K*/AKT/mTOR signalling pathway, leading to abnormal tissue growth and vascular malformations. This variant is known for its association with overgrowth syndromes and other tumours that activate the PI3K signalling pathway [23, 24].

These results are consistent with previous studies that also identified a role for *PIK3CA* mutations. For example, a survey by Andres-Ibarrola *et al.* [25] described a case of a newborn with multifocal congenital haemangiomas with an activating pathogenic *PIK3CA* variant. In addition, a study by Yeh *et al.* [22] confirms the high frequency of *PIK3CA* mutations in pulmonary haemangiomas, suggesting their significant role in the pathogenesis of these conditions. This indicates the need for further research to identify additional factors that may influence the clinical behaviour of haemangiomas.

A study by Mendez *et al.* [26] adds another aspect, pointing to the role of mutations in the vascular endothelial growth factor (*VEGF-A*) and *TIE2* genes, which regulate angiogenesis and vascular stability, contributing to abnormal vessel growth and haemangioma formation. Thus, the studies complement each other, showing that congenital haemangiomas can result from various genetic mutations that affect key cellular signalling pathways.

The placental theory suggests that congenital haemangiomas may be linked to abnormalities in placental vascular development, such as chorioangiomas. These tumours are benign vascular formations that can affect foetal circulation and development. In some cases, large chorioangiomas have been associated with the development of congenital haemangiomas in newborns. A 10-year retrospective study found that newborns with large placental chorioangiomas developed congenital haemangiomas. Out of 175 cases of chorioangioma, 33 children developed a single 4 cm haemangioma on the scalp, and 22 children developed a haemangioma on the sole. This highlights a possible link between placental vascular abnormalities and postnatal vascular lesions [27].

In contrast, a study by Sirotkina *et al.* [28] examines the incidence of IH in newborns according to the presence of chorioangiomas in the placenta. The study included 15,742 placentas, of which 1.08% had chorioangiomas. However, despite the presence of chorioangiomas, no statistically significant difference in the frequency of IH was found between the groups with and without chorioangiomas. Thus, these results highlight that although chorioangiomas may be associated with the development of congenital haemangiomas, their role in the pathogenesis of infantile haemangiomas remains uncertain.

Vascular development abnormalities that underlie congenital vascular formations, including haemangiomas and malformations, are mainly due to mutations in genes that regulate cell proliferation and angiogenesis signalling pathways. In particular, activating mutations in the *GNAQ* and *GNA11* genes trigger the MAPK and YAP signalling cascades, leading

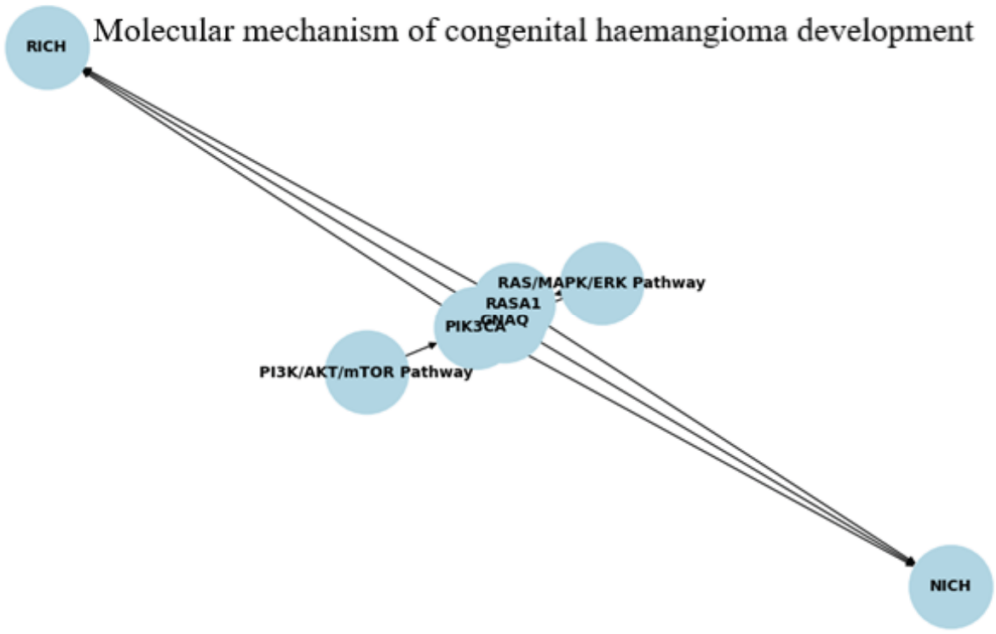

Figure 2: Molecular Mechanism of Congenital Haemangioma Development: PI3K/AKT/mTOR and RAS/MAPK/ERK Signalling Pathways.

Source: compiled by the authors based on [29].

to uncontrolled growth of vascular cells and impaired formation of the vascular bed. At the same time, the activity of the AKT/mTOR pathway, known for its role in angiogenesis and vasculogenesis, can also be disrupted, contributing to pathological vascular growth. Such mechanisms involved in congenital haemangiomas are similar to the pathogenesis of other vascular malformations, for example, capillary-venous and cavernous ones, in which mutations in the *MAP3K3*, *CCM1/2/3* genes that disrupt endothelial cell regulation are also found. Figure **2** illustrates the link between various vascular malformations and genetic mutations [29].

Figure **2** shows how mutations in key genes affect the activation of signalling pathways that regulate cell growth and proliferation. Studies by Ma *et al.* [27] and Butnariu *et al.* [29] agree that congenital haemangiomas are associated with vascular developmental abnormalities, but differ in their mechanisms and causes. Ma *et al.* [27] propose the placental theory, arguing that congenital haemangiomas may be linked to placental vascular abnormalities, such as chorioangiomas, which affect foetal circulation and development. In contrast, Butnariu *et al.* [29] focus on vascular malformations, such as capillary-venous and cavernous lesions, which are caused by mutations in the *MAP3K3*, *CCM1*, *CCM2*, and *CCM3* genes. This aligns with the view of congenital haemangiomas as part of a spectrum of vascular anomalies resulting from disruptions in signalling pathways that regulate endothelial cell growth and differentiation.

Histopathological and immunohistochemical data confirm the vascular nature of congenital haemangiomas, allowing for a deeper understanding of their aetiology. A report by Sasaki *et al.* [30] described an infant who had a purple mass lesion on the right shoulder from birth. Typical morphological features were found: marked vessel dilation, intense hyperaemia, and foci of tissue necrosis. Immunohistochemical analysis showed positive staining for anti-*CD31*, which indicates the presence of endothelial cells, a key component of a haemangioma. Negative staining for anti-*D2-40* and anti-*GLUT1* confirmed the diagnosis of a congenital haemangioma with dilated capillaries. This highlights that vascular development abnormalities play an essential role in the pathogenesis of congenital haemangiomas.

Oestrogen signalling is recognised as an essential contributor to the development of infantile haemangiomas. The expression of oestrogen receptors (ERα and ERβ) is significantly higher during the involution phase than during the proliferative phase, suggesting a regulatory role in both growth and regression. Oestrogens also enhance endothelial proliferation by upregulating *VEGF* expression [31]. Clinical studies support these molecular findings:

Materna-Kiryluk *et al*. [32] reported a female predominance (ratio 1.43), and Alkatan *et al*. [33] found that approximately 60% of periocular haemangiomas occur in girls. Together, these results indicate that female sex hormones, including oestrogen and progesterone (whose receptors also increase during involution), contribute to the angiogenic activity and biological behaviour of infantile haemangiomas.

Hypoxia plays a significant role in the pathogenesis of infantile haemangiomas, acting through several converging molecular pathways. One mechanism involves the induction of *CCN1*, which is highly expressed in proliferative IH and regulates angiogenesis via NF-κB and JNK signalling; suppression of *CCN1* reduces *VEGF-A* expression in haemangioma-derived stem cells [34]. Complementary evidence indicates that hypoxia stimulates HIF-1α, leading to upregulation of *VEGF* and *SDF-1α* and promoting endothelial proliferation. *VEGF*-associated changes in inflammatory cytokines, particularly IL-6, further contribute to proliferative activity [33]. Additional insights from placental studies show that reduced *ACE2* expression under hypoxic conditions enhances *VEGF* signalling and is frequently associated with subclinical chorioamnionitis, reinforcing the link between hypoxia and aberrant angiogenesis [35]. Collectively, these findings demonstrate that hypoxia influences IH development through interconnected pathways involving *CCN1*, *HIF-1α*, *VEG*F, and inflammatory cytokines, highlighting its multifaceted contribution to tumour biology.

Prematurity significantly increases the risk of developing IH in children [36-38]. Research shows that premature infants are more likely to have superficial IH, which are characterised by thicker components and stepped borders. These features correlate with the degree of prematurity: the lower the gestational age, the greater the likelihood of developing thick, superficial IH. The data showed that IH occurred in 75% of children with a gestational age of less than 33 weeks and in 57% of children with a gestational age of 33 to 37 weeks, compared to 50% in full-term infants (p=0.007). In addition, premature infants are more likely to be referred to specialists at a later age, when irreversible skin changes may have already occurred [39]. This was also confirmed in another study by Tanyıldız *et al.* [40], which showed that premature infants and low-birth-weight newborns have an immature vascular system and elevated levels of angiogenic factors, which contribute to abnormal blood vessel growth and the formation of haemangiomas.

However, Tanyıldız *et al.* [40] also add that low birth weight at birth is a risk factor for haemangiomas, including congenital ones, and they explain this by the immaturity of the vascular system and elevated levels of angiogenic factors in premature infants. Both studies complement each other, emphasising the importance of prematurity and related factors in the pathogenesis of haemangiomas. Dankhara *et al.* [41] also indicate that IH is more common in premature infants, especially those born at a gestational age of less than 32 weeks. In a cohort of 1,068,502 eligible infants, the prevalence of IH was 4.7 per 1,000 premature hospitalisations. The study found a significant association between retinopathy of prematurity and IH, suggesting shared pathophysiological mechanisms, such as hypoxia and elevated levels of angiogenic factors, including vascular endothelial growth factor.

In addition to risk factors such as prematurity, hypoxia, mutation, and the influence of oestrogen, other causes of congenital haemangiomas have been found. Klippel-Trénaunay syndrome (KTS) is considered a possible cause of congenital haemangiomas, especially in rare cases involving internal organs such as the gastrointestinal tract, liver, spleen, mediastinum, and genitourinary system. This highlights the need to consider KTS when there are corresponding clinical manifestations in newborns [42]. KTS, initially described as a triad of cutaneous capillary malformation, bony and soft-tissue hypertrophy, and venous and lymphatic malformations, was considered by dermatologists to be a separate diagnostic entity. However, it has become known that KTS is also linked to mutations in the *PIK3CA* gene, which plays a key role in regulating cell growth and angiogenesis. These mutations can lead to abnormal blood vessel growth, which contributes to the formation of haemangiomas [43-45].

A study by Deka *et al.* [46] describes a clinical case of an 11-year-old girl with classic symptoms of KTS, including port-wine stains on her left leg, an enlarged and elongated left leg, soft tissue hypertrophy, and multiple varicose veins. An ultrasound revealed subcutaneous and intramuscular haemangiomas, as well as a rare intraneural haemangioma of the distal posterior tibial nerve. This study highlights that KTS can manifest as various types of haemangiomas, including subcutaneous, intramuscular, and intraneural, underscoring the complex and multifaceted nature of this syndrome.

Furthermore, hyperemesis gravidarum (severe, frequent vomiting during pregnancy) can cause

dehydration and a deficiency of essential trace elements and vitamins in the mother, especially folate, iron, and zinc [47-49]. A lack of these can disrupt foetal angiogenesis and increase the risk of congenital haemangioma by a factor of 1.75 [40]. However, these data conflict with a study by Gong *et al.* [50], where no difference was noted between cases and the control group regarding hypertensive disorders of pregnancy, including hyperemesis (Hyperemesis gravidarum: n=37, %=3.58 in the congenital haemangioma group and n=38, %=3.68 in the control group). This indicates the need for further research to clarify the role of hyperemesis in the development of congenital haemangiomas.

The use of medications during pregnancy has also proven to be an essential factor. In the case of 47 mothers of children with a congenital haemangioma (41.2%) and 28 mothers in the control group (28%), there was a history of taking medication during pregnancy. This increased the risk of developing a congenital haemangioma by a factor of 1.8. However, specific drugs, such as progesterone, analgesics, or antibiotics, did not show a statistically significant association with the development of a haemangioma (p=0.780) [40].

This is supported by a study by Schoch *et al.* [51], which suggests that maternal medication use during pregnancy can also be a significant risk factor for the development of IH. Specifically, the use of progesterone, corticosteroids, and assisted reproductive technologies increased significantly over a 35-year observation period, which correlates with the increase in the frequency of IH. Progesterone, whose use grew from less than 1% to 19%, and corticosteroids, whose use increased from 2% to 12%, showed a statistically significant association with the development of IH. This may influence cellular signalling pathways already disrupted by genetic mutations, leading to increased abnormal blood vessel growth and the development of haemangiomas.

The effect of medication was also considered in a book by Källén [52], which mentions that one of 73 children exposed to lamivudine for the treatment of chronic hepatitis B in early pregnancy had a haemangioma. This emphasises that medication use during pregnancy can be a significant risk factor for the development of haemangiomas, both congenital and infantile. And although a general link exists between medication use during pregnancy and the development of haemangiomas, specific medications may have varying degrees of influence [53-55].

A family history of haemangiomas can also be a risk factor for the development of a congenital haemangioma in children [56, 57]. In 20 out of 114 patients (17.5%) with a congenital haemangioma, there were already cases of haemangiomas or similar lesions in the family. This indicates a possible genetic predisposition to the disease [40]. Meanwhile, in a study by Ariani *et al.* [58], it was described that a family history of haemangiomas or vascular diseases is a significant risk factor for the development of IH. In 27 of 67 patients (40.3%) with IH, there was a family history of vascular disease, whereas in the control group, only 8 of 134 patients (6%) had such a history. Statistical analysis showed a significant difference between the groups ($p<0.05$), indicating a strong association between family history and the development of IH. Thus, a family history of haemangiomas plays an essential role in the development of both infantile and congenital haemangiomas, emphasising the need to consider genetic factors in diagnosis.

Maternal drug use during pregnancy can cause foetal hypoxia and disrupt the regulation of angiogenesis – a key process in the formation of blood vessels - which contributes to the abnormal proliferation of vascular tissue and increases the risk of developing congenital haemangiomas [40, 59, 60]. In contrast, a study by Lind *et al.* [61] found no significant link between opioid use and the development of a haemangioma in children. Among the specific congenital disabilities, a haemangioma did not show a statistically significant association with exposure to opioid analgesics in the first trimester of pregnancy ($p>0.05$). While a theoretical possibility exists, additional research is needed to confirm or refute a link between drug use (including opioids) and the development of haemangiomas.

Overall, the study highlights the importance of considering various factors, such as hyperemesis gravidarum, medication use, family history, and drug use, when assessing the risk of developing congenital haemangiomas. This can contribute to the development of more effective treatment strategies and to improvements in the clinical management of patients with congenital haemangiomas (Table **3**).

The synthesis presented in Table **3** illustrates that congenital haemangiomas arise from the interplay of several biological and developmental influences rather than a single causative factor. Genetic alterations affecting intracellular signalling pathways form an essential part of this landscape. At the same time,

Table 3: Core Aetiological Factors of Congenital Haemangiomas and Evidence

Key factor (analysed systematically)	Underlying mechanism	Synthesised supporting evidence
Somatic mutations in *GNAQ*/*GNA11*	Aberrant G-protein signalling activating MAPK and YAP cascades → uncontrolled endothelial proliferation	Recurrent p.Gln209 substitutions identified across RICH and NICH; consistent functional relevance
PIK3CA activating variants	Activation of PI3K/AKT/mTOR pathway → abnormal vascular growth and tissue overgrowth	Pathogenic variants detected in multifocal CH and vascular overgrowth phenotypes
Mutations in angiogenesis-related genes (e.g., *VEGF-A, TIE2*)	Disruption of angiogenic regulation and endothelial stability	Functional alterations associated with irregular vessel formation
Placental vascular abnormalities	Foetal circulatory disturbances leading to aberrant vascular development	Associations observed in cases with large chorioangiomas, though findings vary by population
Hypoxia-related mechanisms	Induction of HIF-1α, *CCN1*, *VEGF* and SDF-1α → amplified endothelial proliferation	Robust molecular evidence of hypoxia-driven angiogenic signalling
Oestrogen and hormonal influences	ERα/ERβ-mediated upregulation of *VEGF* → enhanced endothelial proliferation	Female predominance and increased receptor expression during involution
Prematurity and low birth weight	Immature vasculature and elevated angiogenic factor expression	Higher frequency of haemangiomas in premature infants and neonates with low birth weight
Family history/hereditary predisposition	Genetic susceptibility affecting angiogenesis regulation	Higher prevalence of haemangiomas among relatives of affected individuals
Syndromic context (e.g., Klippel–Trénaunay syndrome)	*PIK3CA*-related overgrowth spectrum with complex vascular anomalies	Co-occurrence of CH within syndromic overgrowth disorders

hypoxia-related mechanisms, hormonal regulation, and perinatal characteristics contribute additional dimensions that shape vascular behaviour during foetal development. The factors described in the literature do not function in isolation; instead, they appear to intersect at multiple points along angiogenic and vasculogenic processes. Such an integrated overview helps to organise the heterogeneous findings reported across studies and provides a coherent basis for interpreting the diverse clinical presentations of congenital haemangiomas.

4. CONCLUSIONS

This study, aimed at systematising and analysing existing knowledge on the aetiological risk factors for congenital haemangiomas in children, has identified several recurring patterns across genetic, developmental, and environmental domains. By synthesising data from scientific articles, clinical reports, and research monographs, the work consolidated current understanding of the mechanisms and factors associated with the development of congenital haemangiomas.

The analysis indicates that genetic alterations – including mosaic missense mutations in *GNAQ* and *GNA11* and activating variants in *PIK3CA* – represent central mechanisms underlying abnormal endothelial proliferation and vascular development. Additional modifications in angiogenesis-regulating genes, such as *VEGF-A* and *TIE2*, further demonstrate the involvement of disrupted signalling pathways. Hormonal influences, particularly the proliferative effects associated with oestrogen signalling, and hypoxia-related mechanisms involving *CCN1* and HIF-1α activation also contribute to the biological context in which these lesions develop. Perinatal characteristics such as prematurity and low birth weight appear to modify vascular behaviour by impairing the maturation of the angiogenic regulatory system. These findings collectively highlight the multifactorial nature of congenital haemangioma development.

The results of the study provide a foundation for anticipating diagnostic needs and inform potential approaches to personalised management. A more comprehensive understanding of the interplay among genetic factors, prenatal environmental influences, and developmental conditions may help refine diagnostic criteria and support targeted therapeutic decision-making.

The findings point to several avenues for further research. Continued investigation into epigenetic mechanisms – including DNA methylation patterns and histone modifications – may clarify how regulatory

changes influence angiogenesis-related gene expression. Future studies would also benefit from closer examination of maternal physiological conditions during pregnancy. In particular, expanding the focus to include maternal micronutrient status and overall nutritional balance may help to elucidate how deficiencies or altered nutrient availability intersect with angiogenic pathways and foetal vascular development. Further exploration of external environmental exposures and their interactions with genetic predisposition is likewise warranted, as is a detailed assessment of the pharmacological agents used during pregnancy.

The limitations of the study include a limited amount of data on the impact of specific medicinal drugs on the risk of haemangiomas, which makes it difficult to develop precise recommendations for their use during pregnancy. Additionally, the study is limited to published sources, which may not fully reflect all aspects of the aetiology of congenital haemangiomas.

The main directions for future research include an in-depth study of epigenetic changes, such as DNA methylation and histone modifications, and their influence on the expression of genes involved in angiogenesis. It is also necessary to continue research into the impact of external environmental factors, such as exposure to chemicals and infections, on the development of congenital haemangiomas. It is essential to expand the analysis of family history and genetic predisposition to the disease, as well as to study the impact of various pharmacological agents on the risk of haemangiomas.

AUTHORS' CONTRIBUTION

Saltanat Toktosunova conceptualized and designed the study and was responsible for the final manuscript revision. Aitmamat Toktosunov contributed to the methodology, data acquisition, visualization, and critical review of the manuscript. Aliza Imanalieva participated in data collection, literature review, and drafting of the manuscript. Maksim Buhov validated the findings, conducted the data analysis, contributed to the interpretation of the study, and wrote the results section. Arisel Ibraimova assisted with statistical analysis, manuscript editing, and supervised the research process. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors confirm that they have no conflicts of interest.

ETHICS

The study was conducted without human participation. Ethical approval is not required.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available in the article.

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