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Review Article

G protein activation subunit genes in ovarian hemangioma. A systematic review

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Abstract

Background

Heterotrimeric G-proteins transmit signals from G-protein-coupled receptors (GPCRs) to the cell interior, modulating physiological activities based on specific tissue targets. While the fundamental schemes of G-protein regulation and signaling are well-documented, their specific role in rare neoplasms like ovarian hemangiomas remains an emerging area of study. Ovarian hemangiomas are uncommon; most are characterized by isolated reports of peculiar clinical manifestations or morphologic features. To fully characterize the clinicopathologic correlations of ovarian hemangiomas and assess the importance of hormone receptors in their pathogenesis, researchers are increasingly investigating the G protein-activating subunit gene, particularly mutations in *GNAQ*. In other vascular tumors, somatic mutations in these G-protein subunits trigger constitutive activation of downstream pathways, such as MAPK/ERK, driving endothelial proliferation. Understanding these molecular drivers is essential for distinguishing these benign vascular lesions from malignant ovarian cancers and for developing targeted diagnostic markers that bridge the gap between heterotrimeric G-protein signaling and rare gynecological pathology.

Material and Methods

Major databases such as Medline were explored through a detailed literature search, resulting in a systematic review pertaining to G protein activation subunit genes in ovarian hemangioma.

Results

Eight original research scientific articles, dated between 2020 and 2024, about the mentioned topic were highlighted.

Conclusions

Ovarian hemangiomas are extremely uncommon tumors that can occur at any age and are discovered by accident after surgery or autopsy. The purpose of this article is to highlight that these neoplasms should be considered in the differential diagnosis of a hemorrhagic ovarian lesion, even though they are extremely uncommon in the ovary. Receptor-G protein interactions have been the subject of extensive research for over 40 years, yielding significant insights into one of the most fundamental systems in human physiology.

Key words: *Ovarian Hemangioma, vascular tumor, benign ovarian tumor, G protein, GPCR, protein-protein interactions*
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INTRODUCTION

Hemangiomas are benign vascular tumors; however, female genital tract hemangiomas, especially those that form in the

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ovaries, are exceedingly uncommon and are usually identified incidentally at autopsy or after surgery. Even though most are asymptomatic, a small number of these ovarian hemangiomas (OH) may occasionally exhibit symptoms if they are large enough to induce adnexal torsion, cause abdominal pain, or mimic the presentation of an ovarian tumor. As a result, early detection of ovarian cancer remains a critical and pressing issue for women's health. These days, with the quick development of gene chips, transcript sequencing, and large-scale data analysis, scientists have uploaded extensive ovarian cancer-related gene data to the GEO and TCGA databases. Furthermore, there is growing evidence linking the emergence and progression of these malignancies to mutations and aberrant expression of genes such as *SIRT1*, *HBA2*, *BRCA*, *ZWINT*, *SPP1*, and *HBG2*; yet, despite these advancements, the incidence and mortality remain high as these biomarker genes continue to have a poor early diagnostic effect in clinical practice.

This diagnostic challenge is underscored by the complexity of transmembrane signaling networks, which enable all cells to receive information from external stimuli such as hormones, neurotransmitters, or sensory stimuli. Cells can communicate with one another thanks to this basic mechanism, which typically shares two fundamental components: a receptor that identifies an extracellular stimulus and an effector that produces an intracellular signal under the receptor's control. While these components are combined into a single molecule in many systems, such as receptor tyrosine kinases, the G protein-mediated signaling system is comparatively complicated, consisting of an effector, a heterotrimeric G protein, and a receptor. The modular architecture of this system permits convergence and divergence at the interfaces of the G protein and effector, as well as the receptor and G protein, all of which can be independently controlled by other proteins, soluble mediators, or at the transcriptional level.

A vast family of cell-surface receptors known as G-protein-coupled receptors (GPCRs) mediates the effects of numerous physiological ligands and hormones, serving as important targets for medicinal drugs. These functions are mediated by the activation of intracellular G-protein heterotrimers made up of Gα, β, and γ subunits. Specifically, the G proteins are activated upon receptor engagement and then directly interact with downstream enzymes or ion channels to trigger changes in cellular physiology specific to a particular cell type. Within this GPCR signal transduction pathway, the G-protein βγ subunits are necessary for the heterotrimers to interact with the receptor during the nucleotide-exchange reaction. In this process, the G protein α subunit, with firmly bound GDP, is immediately engaged by the receptor; agonist-bound receptors then accelerate the release of GDP to enable GTP binding. This activation causes the Gα subunit to separate from the Gβγ subunits, which remain firmly attached as a constitutive heterodimer.

MATERIAL AND METHODS

"Ovarian" AND "hemangioma" AND "G protein'' were the words used in the MEDLINE database using an advanced search strategy targeting different article categories between 2020 and 2024. The result was 68 articles, out of which we selected 8 articles based on the inclusion criteria. Inclusion criteria were case studies and scientific literature between 2020 and 2024. Exclusion criteria were of scientific literature irrelevant to the specific search. This systematic review was conducted to determine the importance of G protein activation subunit genes in ovarian hemangioma following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Lilacs, Embase, Scopus, and Web of Science were the sources of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL ("Ovarian") AND (hemangioma OR G protein OR GPCRs OR vascular OR lesion OR mutation) AND (genes)]. The following data were collected: first author, year, country of study, type of study, and outcome. The quality of studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist.

RESULTS

Eight articles were included in this systematic review based on the selection criteria. We analyzed and mentioned in the eight articles reviewed. This included only relevant research articles and excluded articles about nonspecific search terms.

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Table 1 – An overview

Author	Title	Journal	Outcome
Jau-Yu Liau, Jia-Huei Tsai, Jui Lan, Chih-Chi Chen, Ying-Hao Wang, Jen-Chieh Lee, Hsuan-Ying Huang	GNA11 joins GNAQ and GNA14 as a recurrently mutated gene in anastomosing hemangioma	Liau JY, Tsai JH, Lan J, Chen CC, Wang YH, Lee JC, Huang HY. GNA11 joins GNAQ and GNA14 as a recurrently mutated gene in anastomosing hemangioma. Virchows Archiv. 2020 Mar;476(3):475-81. doi: 10.1007/s00428-019-02673-y.	GNA11 mutations, as well as its paralogues GNAQ and GNA14, are essential drivers in the pathogenesis of AH
Davide Calebiro, Zsombor Koszegi, Yann Lanoiselée, Tamara Miljus, Shannon O'Brien	G protein-coupled receptor-G protein interactions: a single-molecule perspective.	Calebiro D, Koszegi Z, Lanoiselée Y, Miljus T, O'Brien S. G protein-coupled receptor-G protein interactions: a single-molecule perspective. Physiological reviews. 2021 Jul 1;101(3):857-906. doi: 10.1152/physrev.00021.2020.	G protein-coupled receptors (GPCRs) regulate many cellular and physiological processes, responding to a diverse range of extracellular stimuli.
Daniela Nakuci, Erisa Kola, Edlira Horjeti, Ina Kola, Blerona Shaipi, Juna Musa, Ali Guy, Mehdi Alimehmeti	Ovarian Hemangioma Presented as an Incidental Ovarian Mass: A Rare Case Report along with Literature Review	Nakuci D, Kola E, Horjeti E, Kola I, Shaipi B, Musa J, Guy A, Alimehmeti M. Ovarian hemangioma presented as an incidental ovarian mass: a rare case report along with literature review. Archives of Clinical and Medical Case Reports. 2020 Sep 3;4(5):760-5. DOI: 10.26502/acmcr.96550262	Hemangiomas of the ovary are very rare neoplasms with a wide age range.
Dehua Yang, Qingtong Zhou, Viktorija Labroska, Shanshan Qin, Sanaz Darbalaei, Yiran Wu, Elita Yuliantie, Linshan Xie, Houchao Tao, Jianjun Cheng, Qing Liu, Suwen Zhao, Wenqing Shui, Yi Jiang & Ming-Wei Wang	G protein-coupled receptors: structure- and function-based drug discovery	Yang D, Zhou Q, Labroska V, Qin S, Darbalaei S, Wu Y, Yuliantie E, Xie L, Tao H, Cheng J, Liu Q. G protein-coupled receptors: structure-and function-based drug discovery. Signal transduction and targeted therapy. 2021 Jan 8;6(1):7. https://doi.org/10.1038/s41392-020-00435-w	The most successful therapeutic target families, G protein-coupled receptors (GPCRs)
Philipp Jansen, Hansgeorg Müller, Georg C	GNA14, GNA11, and GNAQ	Jansen P, Müller H, Lodde GC, Zaremba A, Möller I, Sucker A,	These mutations were not identified in

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Lodde, Anne Zaremba, Inga Möller, Antje Sucker, Annette Paschen, Stefan Esser, Jörg Schaller, Matthias Gunzer, Fabian Standl, Sebastian Bauer, Dirk Schadendorf, Thomas Mentzel, Eva Hadaschik, Klaus G Griewank	Mutations Are Frequent in Benign but Not Malignant Cutaneous Vascular Tumors	Paschen A, Esser S, Schaller J, Gunzer M, Standl F. GNA14, GNA11, and GNAQ mutations are frequent in benign but not malignant cutaneous vascular tumors. Frontiers in genetics. 2021 Apr 30;12:663272. doi: 10.3389/fgene.2021.663272	malignant vascular tumors, which could be of potential diagnostic value in distinguishing these entities.
Nadia Arang, J Silvio Gutkind	G Proteins and G Protein-Coupled Receptors as Cancer Drivers	Arang N, Gutkind JS. G protein-coupled receptors and heterotrimeric G proteins as cancer drivers. FEBS Letters. 2020 Dec;594(24):4201-32. doi: 10.1002/1873-3468.14017	Understanding the complex mechanisms underlying cancer initiation and progression, GPCRs will play an increasingly significant role
Mingyang Zhang, Ting Chen, Xun Lu, Xiaobing Lan, Ziqiang Chen & Shaoyong Lu	G protein-coupled receptors (GPCRs): advances in structures, mechanisms, and drug discovery	Zhang M, Chen T, Lu X, Lan X, Chen Z, Lu S. G protein-coupled receptors (GPCRs): advances in structures, mechanisms and drug discovery. Signal transduction and targeted therapy. 2024 Apr 10;9(1):88. https://doi.org/10.1038/s41392-024-01803-6	GPCR-druggable allosteric sites can guide structure- or mechanism-based drug design and future therapeutic potential of targeting this receptor family.
Sebastjan Merlo, Gregor Vivod, Barbara Gazic, Nina Kovacevic	Anastomosing hemangioma of t ovary – comprehensive revie of this rare ovari entity	Merlo S, Vivod G, Gazic B, Kovacevic N. Anastomosing hemangioma of the ovary–a comprehensive review of this rare ovarian entity. Radiology and Oncology. 2024 Sep 15;58(3):320. doi: 10.2478/raon-2024-0050	Preliminary imaging and initial microscopic examination reveal benign behaviour.

DISCUSSION

Hemangiomas are benign tumors of blood vessels occurring due to malformation of blood vessels during canalization, leading to abnormal channels. Ovarian hemangioma (OH) can develop at various ages, spanning from toddlers at 2 years to the elderly at 81 years.1

Histologically, OH has three types depending on the size of the blood vessels: cavernous, capillary, and a mixed type. Cavernous are the most common type, while the other two occur less frequently.2

The various differential diagnoses include sclerosing stromal tumor and microcystic stromal tumor. Clinically, OH can mimic ovarian carcinoma when patients present with elevated CA-125 and ascites and pseudo-meigs.3

Other differentials of OH include tubo-ovarian mass, twisted ovarian cyst, chocolate cyst, and pathologically they are

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distinguished from vascular growths, lymphangiomas, and monodermal teratomas.4

The authors described an autopsy that identified small, synchronous hemangiomas of the ovary and cervix. Similar cases of hemangiomas involving the ovary had been reported, usually as an unexpected finding.5

Kasabach-Merritt (also known as hemangioma with thrombocytopenia) presents as a vascular tumor and consumptive thrombocytopenia or coagulopathy that can lead to fatal internal bleeding.6

Numerous case reports have described a unilateral or bilateral ovarian hemangioma and massive ascites that prompted clinical suspicion of a primary ovarian malignancy.7

A true ovarian hemangioma is a mass of vascular channels of variable sizes with minimal stroma, which is reasonably circumscribed and distinct from the remaining ovary or involving the ovary almost entirely.8

They are usually unilateral and most often in the medulla and hilus. The origin of ovarian hemangioma is controversial.9

Mechanisms and Hormonal Impact: Stromal luteinization in ovarian hemangioma is hypothesized to result from either mechanical pressure from the tumor or the secretion of stroma-stimulating substances. This process produces androgens that convert to estrogen, potentially leading to hyperandrogenism, endometrial hyperplasia, or carcinoma.10

Hypothesis Limitations: The mechanical theory is challenged by evidence that luteinization can occur in the unaffected contralateral ovary and is not always proportional to tumor size. Some small hemangiomas exhibit significant stromal reactions while larger lesions do not, suggesting mechanical action is not the sole driver.11

Anastomosing hemangioma is a rare benign vascular tumor reported to occur in the kidney, testis, paravertebral soft tissue, gastrointestinal tract, liver, and, in rare instances, in the ovary.12

The genetic hallmark of AH is GNAQ hotspot mutations at codon 209 in 45-69% of cases, while other less common genotypes have been reported, such as GNA14 and GNA11 mutations.13

Other benign vascular neoplasms harboring GNA mutations - GNAQ, GNA14, and GNA11 encode G-protein subunits which are part of the alpha q subfamily of G proteins, with GNA14 and GNA11 being paralogs of GNAQ.14

These G-proteins mediate the signaling of G-protein-coupled receptors, and the downstream result is the activation of MAP kinase pathways, which control cell proliferation.15

This suggests the possibility of molecular heterogeneity among these rare hemangioma variants and raises skepticism about the diagnostic utility of *GNA* mutations in this hemangioma spectrum.16

Many of these have historically been considered reactive lesions, but more recent genetic studies have demonstrated clonal pathogenic mutations in some, suggesting a neoplastic nature.17

Interestingly, alterations in this family have been reported in other benign vascular tumors. Recurrent mutations at codon 209 of *GNAQ* and *GNA11* have been found in the majority of congenital hemangiomas.18

G protein-coupled receptors (GPCRs) represent the largest and most diverse family of cellular receptors in eukaryotes. Of the 800 GPCRs encoded in the human genome.19

The remaining receptors mediate the effects of a wide range, including light, ions, metabolites, hormones, and neurotransmitters. The main function of membrane receptors is to relay extracellular signals to the cell interior, allowing cells to communicate with each other and sense the extracellular environment.20

In contrast, GPCRs rely on their interaction with G proteins to transmit signals to membrane-bound effectors, including ion channels and enzymes. They play a critical role in ensuring the high flexibility, sensitivity, and specificity observed in GPCR signaling.21

G proteins represent the largest family of cell surface receptors, with over 35 G protein subunits involved in the transduction of diverse signaling cascades.22

These receptors play key roles in many cellular and physiological functions, including neurotransmission, cardiac response, and blood pressure regulation, vision, olfaction, tissue development, and immune regulation.23

The human GPCR superfamily can be phylogenetically grouped into 5 subfamilies based on distinct structural features— Class A (rhodopsin), Class B1 (secretin), Class B2 (adhesion), Class C (glutamate), and Class F (frizzled/taste2).24

GPCR activation is initiated by the binding of an agonist ligand to the extracellular domain of the receptor, which induces a rapid conformational change in the extracellular and intracellular loops of the receptor.25

As GPCRs and their associated G proteins are involved in a diverse array of signal transduction pathways and cellular processes, dysregulation in either can have significant

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impacts on cellular behaviour and the initiation of pathogenic processes.26

This is highlighted by a large body of drugs in the market targeting GPCRs. Indeed, 34% of all FDA-approved drugs currently on the market target GPCRs directly or indirectly.27

GPCRs play a fundamental role in human physiology, participating in the control of virtually all physiological functions, including neurotransmission, hormone release, heart contractility, and immune responses.28

Intriguingly, the appearance of GPCRs and their signaling machinery, such as G proteins, arrestins, and regulators of G protein signaling (RGS) proteins, predates the development of the nervous system.29

Perhaps the best evidence for a role of GPCRs in cell-cell communication in unicellular eukaryotes comes from studies of colony formation in the amoeba Dictyostelium discoideum.30

Upon starvation, Dictyostelium uses cyclic AMP (cAMP) as a chemoattractant to induce colony aggregation and the formation of multicellular structures that can withstand harsh environmental conditions.31

Although a small number of GPCRs are found in ancestral eukaryotes, and G proteins are highly conserved between unicellular holozoans and metazoans, 32

It was indeed the development of specialized cell types devoted to cell communication, such as neurons and endocrine cells, that likely fostered the flourishing of the GPCR superfamily, ultimately placing it center stage in human physiology and disease.33

The fundamental role of GPCRs as receptors for several pituitary hormones and hypothalamic release factors. All major known hypothalamic releasing hormones and inhibiting factors, including somatostatin and dopamine, act via specific GPCRs.34

Similarly, all anterior and posterior pituitary hormones, except for the growth hormone and prolactin, signal through the activation of GPCRs.35

Many of the physiological effects of these hormones are mediated via activation of the Gs protein and the resulting stimulation of cAMP/PKA signaling.36

Consequently, alterations of key elements of these signaling pathways, for instance, caused by genetic mutations, are frequently found in endocrine disease.37

A structurally diverse repertoire of ligands, from photons to many hormones and neurotransmitters, activate GPCRs to elicit their physiological functions.38

Heterotrimeric G-proteins directly relay the signals from GPCRs. These G-proteins are composed of α, β, and γ subunits. The β and γ subunits are tightly associated and can be regarded as one functional unit.39

G-proteins function as molecular binary switches, with their biological activity determined by the bound nucleotide. Upon agonist binding, GPCRs increase the exchange of GDP bound on the Gα subunit with GTP.40

This leads to the dissociation of the Gα subunit from the Gβγ dimer, resulting in two functional subunits (Gα and Gβγ). Both Gα and Gβγ subunits signal to various cellular pathways.41

Modern molecular studies have confirmed that nearly all anastomosing hemangiomas of the ovary harbour recurrent somatic mutations in heterotrimeric G-protein alpha-subunit genes, specifically GNAQ, GNA11, and GNA14.42.

Mutations are highly specific to "hotspot" locations that impair the protein's ability to return to an inactive state. For GNAQ and GNA11, this occurs at codon 209, while GNA14 mutations typically occur at codon 205.43

These activating mutations cause the G-protein to remain in a "constitutively active" GTP-bound state. This leads to continuous triggering of downstream pathways—most notably the MAPK/ERK signaling pathway—which drives the uncontrolled proliferation of endothelial cells that form the tumor.44

Identifying G-protein subunit mutations provides a critical diagnostic tool. These mutations are highly frequent in benign hemangiomas but are generally absent in malignant angiosarcomas, allowing clinicians to distinguish these rare benign lesions from aggressive ovarian cancers.45

Unlike many malignant ovarian tumors that feature high genomic instability (e.g., *TP53* or *BRCA* mutations), ovarian hemangiomas are "genetically simple."46

They are often driven by these single G-protein mutations without additional pathogenic alterations, confirming they are true clonal neoplasms rather than reactive processes.47

G-protein activating subunit gene mutations are the definitive drivers behind rare ovarian hemangiomas. These somatic mutations, primarily occurring in GNAQ, GNA11, or GNA14, trigger constitutive signaling that leads to the clonal proliferation of vascular endothelial cells.48

Beyond confirming the neoplastic nature of these tumors, identifying these G-protein alterations serves as a vital diagnostic benchmark, enabling clinicians to accurately distinguish benign ovarian hemangiomas from malignant mimics like angiosarcoma, which typically lack these specific genetic drivers.49

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This molecular shift from descriptive pathology to genetic identification offers new potential for targeted management and a deeper understanding of rare gynecological vascular lesions.50

CONCLUSION

Uncommon vascular tumors in the female vaginal tract are called ovarian hemangiomas. Less than 60 cases have been reported, affecting people of all ages, from young children to the elderly. They can resemble malignant ovarian tumors and produce acute abdominal pain due to ascites or ovarian torsion. They are frequently asymptomatic and found by accident during surgery or autopsy. Comprehensive histopathological and immunohistochemical analyses are necessary for accurate diagnosis and treatment. G-proteins play a crucial role in transmitting signals from GPCRs to the interior of cells, impacting a range of physiological and biochemical processes. Their regulation and signaling, including their interactions with non-GPCRs and physiological roles that are difficult to explain by established pathways, are still being investigated. The cause of ovarian hemangiomas, especially the anastomosing subtype, is recurrent somatic activating mutations in G-protein alpha-subunit genes, namely GNAQ, GNA11, and GNA14. The detection of these G-protein changes provides a conclusive molecular marker that separates benign ovarian hemangiomas from malignant mimics, such as angiosarcoma, which usually do not have these mutations. In the end, knowledge of these subunit gene changes has changed the clinical view of ovarian hemangiomas from accidental discoveries to acknowledged clonal neoplasms, providing a crucial diagnostic standard for precise pathological assessment and patient care.

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Conflict of interest

The author declares no conflict of interest.

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