

Review

Assessment of Genetic Profiling in Gestational Trophoblastic Neoplasia Cases is an Innovative Prognostic Tool for Stratification of Malignant or Benign Tumors: A Systematic Review Study

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Abstract: *Rationale* — Gestational trophoblastic neoplasia (GTN) is an abnormal proliferation of placental trophoblastic cells, often with fatal outcome as metastasis. The remarkable role of genetic alterations in GTN has been scientifically confirmed. Therefore, this systematic review aimed to collect all the genes involved in GTN, evaluate the genetic risk stratification in GTN cases, and consider all the chemoresistance mutations for early diagnosis and accurate treatment of GTN patients.

Methods — A systematic search was performed in validated databases (PubMed, Scopus, WoS, ScienceDirect, Embase, and Google Scholar) using the main MeSH keywords: “gene expression”, “gene mutation”, “gene alteration”, “gestational trophoblastic neoplasia”, “GTN”, “chemoresistance”, and “risk stratification”. To select articles based on the inclusion and exclusion criteria, we followed the PRISMA 2020 guidelines, specifically: primary and secondary screening, resolving duplication, and qualification of articles according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guiding principles. Finally, all articles reporting the role of gene expression changes in GTN were reviewed for data extraction and sorting.

Results — Initially, 458 articles were retrieved from the databases, and 365 duplicates were eliminated. During the primary and secondary assessment, 24 and 23 irrelevant articles were excluded, respectively. Finally, 27 moderate- and high-quality studies were selected for assessment. The results of the study showed that aberrant gene expression, mutations, and DNA methylation in 13 validated genes (including maspin, MCL-1, COX4I1, GnT-IVa, ASPPI, SNRPN, MEST, c-erbB-2, mutant p53, NLRP7, KHDC3L, MTHFR) were involved in the development of GTN. Also, mutations in four genes (maspin, m-p53, NLRP7, and KHDC3L) were associated with a high risk of developing GTN. In addition, a mutation in the NLRP7 gene could lead to the development of chemoresistance in GTN treatment.

Conclusion — Laboratory assessment of some specific genes in patients can facilitate rapid diagnosis and timely treatment of GTN cases.

Keywords: gene expression, gene mutation, gestational trophoblastic neoplasia, chemoresistance, risk stratification, systematic review.

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Introduction

Gestational trophoblastic neoplasia (GTN) is a rare and serious complication resulting from abnormal growth of trophoblastic tissue, often following molar pregnancy, miscarriage, or even normal pregnancy. GTN also leads to progression to malignancy. Thus, clinical manifestations of GTN include abnormal vaginal bleeding, high beta-human chorionic gonadotropin (β -hCG) levels, and metastasis-like symptoms in advanced cases [1]. Although the exact mechanism of GTN is unclear, it is associated with critical genetic mutations and alterations [2]. GTN is classified into low-risk and high-risk categories based on the International Federation of Gynecology and Obstetrics (FIGO) staging and the World Health Organization (WHO) prognostic scoring system. Low-risk GTN is defined as WHO score ≤ 6 pts and FIGO stages I-III with high sensitivity to chemotherapy (100% cure rate) [3]. In contrast, high-risk GTN is characterized by WHO score ≥ 7 pts and FIGO stage IV requiring multi-agent chemotherapy (resistant to chemotherapy, relapse rate is 30-40%) [4], as well as poor prognosis [5]. GTN can

also be classified into benign and malignant. Benign GTN includes placental site nodules and hydatidiform moles (HMs). Malignant GTN includes four subtypes: invasive hydatidiform mole, gestational choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [6]. Alterations in gene expression play a critical role in the pathogenesis and progression of GTN, affecting both benign and malignant forms. Studies have confirmed that changes in gene expression profiles, especially those related to trophoblast differentiation and growth regulation, play a critical role in the development of GTN [7].

Extensive research is being undertaken to diagnose different types of GTN and determine adequate therapeutic strategies. Although recent studies have shown that alterations in gene expression may contribute to the pathogenesis of GTN, no systematic review on this issue has been published yet. Therefore, the authors of this article have compiled all the genes involved in the development and severity of GTN. The authors believe that genetic evaluation of GTN tissue samples may contribute to a

more accurate diagnosis of the disease and, consequently, the selection of more appropriate therapeutic approaches. The main novelty of this systematic review is the identification of genes involved in the pathogenesis of GTN, as well as the listing of genes associated with the development of chemoresistance to GTN treatment.

Methods

Search objective and strategy

Objective: This systematic review was designed to collect all comprehensive studies reporting the association between gene expression and the occurrence of GTN. For the search strategy, relevant keywords were identified using Medical Subject Headings (MeSH) terms including “gene expression”, “gene mutation”, “gene alteration”, “gestational trophoblastic neoplasia”, “GTN”, “chemoresistance”, and “risk stratification”. The search strategy was designed as follows: (“gene expression” OR “gene mutation” OR “gene alteration”) AND (“gestational trophoblastic neoplasia” OR “GTN”) AND (“chemoresistance”) AND (“risk stratification”). The search process was applied in valid English language databases PubMed, Scopus, WoS, ScienceDirect, and Embase. Finally, Google Scholar search engine and references of all included articles were manually screened to achieve the maximum number of relevant studies. No time limit was considered, and all relevant articles were included by February 1, 2025 (search strategy was updated on April 24, 2025), and all steps of article selection were

performed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [8].

Inclusion and exclusion criteria

Regarding the inclusion criteria, all English-language publications (cross-sectional, cohort, case-control, case study, and original articles) reporting genetic findings in GTN cases (gene expression, gene mutation, and DNA methylation) were fully included in the data extraction process. In addition, reviews, case reports, case series, animal studies, and articles in other languages were excluded from our study [9].

Article screening

After collecting the articles, all references were imported into EndNote citation management software (version 8x, USA). Duplicate articles were detected and taken care of. The title and abstract of the remaining articles were then assessed based on the inclusion and exclusion criteria (primary screening). In the next step (secondary screening), the full texts of the articles were assessed based on the inclusion/exclusion criteria. All screening steps were performed by two independent investigators (AEJ and SAZJ), and the corresponding author (SNH) was responsible for resolving any potential conflicts or disagreements. All article screening processes were conducted according to the PRISMA 2020 flow diagram (Figure 1) [10].

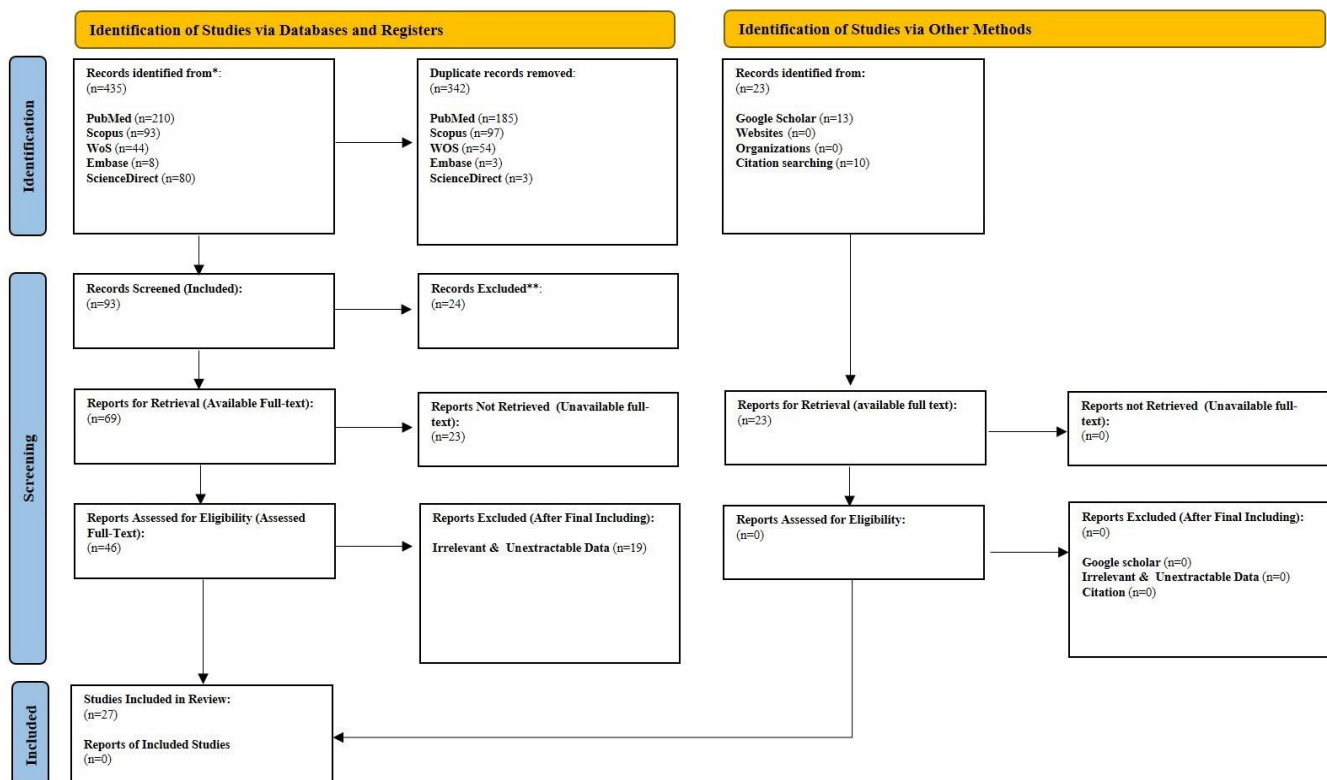


Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources.

Article quality control

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to assess the quality of the studies based on 6 main scales and 32 different subgroups. Based on the STROBE score, publications were classified into low-quality (0-15 pts) and high-quality (16-32 pts) articles. All studies of moderate and high quality (STROBE score \geq 16 pts) were fully included in the data extraction procedure [11].

Data extraction and categorization

After selecting the relevant articles, various data were extracted (on the abnormal gene expression in GTN cases, abnormal mRNA expression in GTN cases, and critical genes involved in risk stratification of GTN progression) as listed below.

Results

PRISMA- and STROBE-based article selection results

After the initial search, 435 primary articles were retrieved from validated databases, such as PubMed (n=210), Scopus (n=93), WoS (n=44), ScienceDirect (n=80), Embase (n=8), Google Scholar (n=13), and references in other published sources (n=10). The references were imported into EndNote software, and 365 duplicates were eliminated. Based on the inclusion and exclusion criteria, 24 and 23 articles were excluded during the primary and secondary screening, respectively; 19 low-quality studies were also excluded. Ultimately, 27 eligible moderate- and high-quality studies focusing on the genetic basis of GTN were selected for data extraction and categorization ([Figure 1](#)). The data were categorized into two main topics (epigenetic changes in GTN and gene mutations in GTN) as well as various subtopics.

Epigenetic changes in GTN

Abnormal gene expression in GTN. Studies have shown that disruption of epigenetic marks in differentially methylated regions (DMRs) can result in abnormal gene expression, yielding severe phenotypic changes such as GTN [12], including maspin, myeloid cell leukemia-1 (MCL-1), and cytochrome c oxidase subunit 4 isoform 1 (COX4I1) ([Supplement 1](#)).

Maspin. Mammalian serine protease inhibitor (maspin), a tumor suppressor gene, exhibits altered expression in gestational trophoblastic disease (GTD). In normal human placenta, maspin is expressed in trophoblast cells and may act as an inhibitory regulator of trophoblastic invasion. Studies have shown that maspin expression is downregulated in GTD, especially in cases of GTN, suggesting its role in the pathogenesis and malignant transformation of hydatidiform mole [13]. Immunohistochemical staining shows that the percentage of stained trophoblast nuclei in both complete and partial HMs is significantly ($P < 0.001$) lower than that in normal first-trimester placentas. However, no significant difference ($P > 0.05$) was found in immunostaining between complete and partial HMs [14]. In addition, decreased maspin expression is observed in choriocarcinoma and placental site trophoblastic tumors. Compared with normal placenta, maspin expression is decreased in GTD ($P < 0.05$). Also, maspin expression is inversely correlated with serum β -hCG levels, uterine size, and theca lutein cyst diameter in MF. In a study of 48 normal first-trimester placentas, 49 resolved HMs, 39 malignant HMs, and 11 invasive HMs or choriocarcinomas, low maspin⁺ expression was

found vs. normal first-trimester placentas, resolved HMs, malignant HMs, and invasive HMs/choriocarcinomas [15]. Maspin expression was localized in the cytoplasm of trophoblastic cells, with higher expression in cytotrophoblasts vs. syncytiotrophoblasts [16]. The combination of maspin and mutant p53⁺ expression showed 84% specificity, 76% positive predictive value, and 70% negative predictive value for the development of GTN. The absence of maspin expression provided 74.10% sensitivity and 65.31% specificity for the development of GTN, while m-p53⁺ expression provided 74.36% sensitivity and 53.06% specificity. These data suggest that maspin expression patterns in combination with other markers, such as m-p53, may help predict the risk of developing GTN in patients with HMs.

Mitochondrial transcripts. MCL-1, an anti-apoptotic gene, plays an important role in the pathogenesis and clinical manifestations of GTN. A study of HMs (progressing to GTN) vs. resolved HMs revealed higher expression of MCL-1 in HMs developing to GTN [18]. This study confirmed that MCL-1 RNA and protein expression levels were significantly higher in HMs developing to persistent disease requiring chemotherapy. MCL-1 immunoreactivity, predominantly detected in cytotrophoblasts, correlated with the apoptotic index. These data suggest that MCL-1 may serve as a useful marker for predicting the clinical manifestations of HMs [19].

COX4I1 regulates trophoblast cell proliferation, migration, and invasion by modulating mitochondrial function. Low COX4I1 expression results in mitochondrial dysfunction in the extravillous trophoblasts (EVT), leading to altered trophoblast function and ultimately pregnancy loss [20].

Abnormal mRNA expression in GTN. Expression of mRNA has been studied in GTN and related diseases, revealing key molecular features and potential biomarkers. MicroRNAs (miRNAs) play key roles in cancer initiation and progression of GTN, including N-acetylglucosaminyltransferase IVa (GnT-IVa), apoptosis-stimulating protein p53-1 (ASPP1), small nuclear ribonucleoprotein polypeptide N (SNRPN), mesoderm-specific transcript (MEST), and c-erbB-2 ([Supplement 1](#)).

GnT-IVa. GnT-IVa plays a significant role in the progression and malignancy of GTN, particularly choriocarcinoma. GTN (formed as a result of malignant transformation of placental trophoblast) secretes human hCG, similar to normal placenta and HMs [21]. An immunohistochemical study revealed intense staining of GnT-IVa in trophoblastic cells of invasive HM and choriocarcinoma. Overexpression of GnT-IVa in choriocarcinoma cells can intensify cell migration and invasion by 2.5 and 1.4 times, respectively, and also enhance the ability to adhere to extracellular matrix components. These data indicate that GnT-IVa is involved in the regulation of choriocarcinoma invasion [22].

ASPP1. ASPP1, a proapoptotic protein belonging to the p53 apoptosis-stimulating protein (ASPP), plays an important role in the development of GTD. ASPP1 stimulates apoptosis through interaction with p53. Studies have demonstrated a significant decrease in ASPP1 mRNA and protein levels in HMs and choriocarcinomas vs. normal placentas, as assessed by quantitative PCR and immunohistochemistry assays. The decrease in ASPP1 levels correlates with hypermethylation of this gene, suggesting that hypermethylation is likely a mechanism for the downregulation of ASPP1 in GTN. Lower ASPP1 immunoreactivity was also observed in HMs progressing to persistent GTN ($P = 0.045$). Furthermore, ASPP1 expression statistically significantly correlates

with proliferative indices (Ki67 and MCM7), apoptotic activity (M30 CytoDeath antibody), and p53 and caspase-8 immunoreactivity. These data suggest that downregulation of ASPP1 through hypermethylation may contribute to the pathogenesis and progression of GTD, potentially through a concomitant effect on apoptosis [23].

Imprinted genes. Studies show that the paternal genome significantly influences placental development, as evidenced by the higher expression frequency of paternal genes in the placenta. These genes are typically regulated by cis-acting DMRs, which can also be associated with differential histone marks.

SNRPN. SNRPN is a paternal gene expressed with a growth-promoting phenotype. It is involved in pre-mRNA processes such as tissue-specific alternative splicing. SNRPN, along with PEG10 and MEST, is poorly understood in the process of placentation, despite its key role in tumorigenesis. According to the study, SNRPN mRNA expression decreases as pregnancy progresses, exhibiting a 4.4–5.7-fold reduction after mid-pregnancy ($p < 0.001$). SNRPN expression was also 3.3 times higher ($p < 0.05$) in maternal blood leukocytes collected from the molar vs. the first trimester group. In molar pregnancy, SNRPN DMR methylation was lower in placental villi than in maternal blood, resulting in decreased methylation in maternal plasma, suggesting that SNRPN is a potential epigenetic marker specific for HM. The development of preeclampsia was associated with a 1.3-fold ($p < 0.05$) increase in SNRPN methylation in maternal blood compared with normal blood in the third trimester; while HM was associated with a 1.26-fold ($p < 0.05$) and 1.33-fold ($p < 0.01$) reduction in SNRPN methylation vs. normal blood in the first and second trimesters, respectively. Strong direct correlation was found between the mRNA expression levels of these imprinted genes among the placental villi ($p < 0.01$). According to the study, a significant association was found between low DNA methylation/H3K27me3 level and higher SNRPN expression in highly proliferating normal placenta in early pregnancy. In placental villi characterized by HM, aberrant changes in methylation levels in the DMRs of these genes were observed, resulting in higher SNRPN expression. MEST and SNRPN DMRs have the potential to act as novel markers of fetal DNA in maternal plasma. Hence, variations in methylation levels in these DMRs regulate normal placentation and placental disorders [12].

DNA methylation. DNA methylation plays an important role in the occurrence and development of GTN. Studies have shown that DNA methylation increases with disease severity in GTD, affecting the expression of genes associated with villous trophoblast differentiation [24].

MEST. The MEST gene, highly expressed in the placenta, induces angiogenesis of placental trophoblast and decidua. HM villi exhibit higher MEST expression, while choriocarcinoma cells exhibit lower expression. These findings shed light on the molecular pathways of GTD, potentially facilitating the development of new diagnostic and therapeutic tools. Choriocarcinoma samples exhibit the highest DNA methylation, while villous trophoblasts exhibit the lowest. The DNA methylation level in complete HM is between that of placenta and choriocarcinoma [12].

c-erbB-2. In patients with simple molar pregnancy, gynecologists are concerned about the possibility of progression to GTN. As a member of the epidermal growth factor receptor family, c-erbB-2 is involved in the pathogenesis of malignancies, including

GTN [25]. Hasanzadeh et al. found increased c-erbB-2 expression in cytotrophoblast from patients with GTN [26] with a cutoff value of 12.5% for cytotrophoblast with membranous c-erbB-2 staining, a sensitivity of 90%, and a specificity of 92%, which may increase the risk of progression of HM to GTN [27].

Gene mutations in GTN

According to published studies, some specific gene mutations may potentially lead to the development of GTN. These mutations are usually inherited in an autosomal recessive manner [28], including mutant p53 (m-p53), NLR family pyrin domain containing 7 (NLRP7), KH domain-containing protein 3-like (KHDC3L), and methylenetetrahydrofolate reductase (MTHFR) C677T ([Supplement 1](#)).

Mutant p53 (m-p53). The expression patterns of m-p53 are associated with the development of GTN. A study by Sun et al. evaluated maspin and m-p53 expression in GTD and their role in predicting the development of GTN. Immunohistochemistry was used to detect maspin and m-p53 expression in 48 normal first-trimester placentas matched for gestational age from 49 HMs that had regressed, 39 malignant HMs, and 11 invasive moles or choriocarcinomas. The results showed that m-p53 expression levels were elevated in GTD placentas compared with normal placentas ($P < 0.05$) [14]. The frequency of m-p53⁺ expression was significantly higher in patients with late FIGO stages (FIGO stage \geq III) compared with those with early stages (FIGO stage \leq II; 87.9% vs. 58.8%; $P = 0.019$) [14]. Maspin⁺ and m-p53⁺ expression exhibited 84% specificity, 76% positive predictive value, and 70% negative predictive value for the development of GTN. These data suggest that maspin⁺ and m-p53⁺ expression is associated with the development of GTN in patients with HM. However, Chen et al. found rare mutations in the tumor suppressor gene p53 in GTN [29]. Hasanzadeh et al. found that p53 expression was significantly increased in the cytotrophoblast and syncytiotrophoblast of GTN and complete HMs [26].

NLRP7. Mutations in the NLRP7 gene, usually inherited in an autosomal recessive manner, have significant consequences in recurrent HM (RHM) and GTN [30]. Although GTD typically occurs sporadically, in approximately 0.1% of pregnancies, genetic mutations such as those in NLRP7 can increase the risk of RHM, with the risk of recurrence increasing with each subsequent molar pregnancy [28]. In approximately 60% of patients with a history of two HMs, NLRP7 gene mutations are associated with other adverse obstetric outcomes [31]. In malignant trophoblast cells, NLRP7 is frequently overexpressed and regulates the expression of HLA-G [32] and PD-L1 [33], which enhances maternal immune tolerance and masks tumor cells, creating an anti-inflammatory environment favorable for tumor growth. NLRP7 overexpression can also mediate excessive proliferation of trophoblast cells by suppressing their differentiation and leading to metastasis [34].

KHDC3L. Mutation in the KHDC3L gene is associated with RHM, a rare pregnancy complication characterized by abnormal trophoblast proliferation [35]. NLRP7 and KHDC3L are maternal-effect genes implicated in RHM [36]. A study of 14 Iranian patients with RHM found a common KHDC3L mutation, c.1A>G, in four patients with the same haplotype [37].

MTHFR C677T. The role of the C677T polymorphism in MTHFR gene in HTN is under study, with some publications suggesting an impact on the outcome of methotrexate treatment [38]. The study presents a case of postmolar pregnancy, where the C677T

mutation in MTHFR required a change in chemotherapy regimen. This case highlights the lack of established guidelines for the treatment of gynecologic malignancies in patients with the MTHFR allele, emphasizing the need for an individualized approach [39]. In addition, the presence of the MTHFR C677T polymorphism in HM tissue predicts the failure of methotrexate treatment in low-risk GTN. However, according to Lasecka et al., the 667C>T and 1298A>C polymorphisms of the MTHFR gene did not predict the response to methotrexate in patients with GTN. The C667T allele is associated with reduced efficacy and increased toxicity when using methotrexate [40].

Critical genes involved in risk stratification of GTN progression

Maspin. Maspin expression in patients with MF is associated with a lower risk of developing GTN. The absence of maspin expression had 74.10% sensitivity and 65.31% specificity in predicting the development of GTN [14].

M-p53. Expression of m-p53 in patients with HM is associated with a higher risk of developing GTN. The presence of m-p53 expression had 74.36% sensitivity and 53.06% specificity in predicting the development of GTN [14].

NLRP7. In rare cases, RHM with or without postmolar GTN may have a genetic cause (NLRP7 mutation) with an autosomal recessive pattern of inheritance. NLRP7 mutation is present in approximately 60% of patients with a history of two molar pregnancies and is associated with other adverse obstetric outcomes. Mutation of this gene can lead to chemoresistance to treatment of GTN [41].

KHDC3. There are also some genetic mutations associated with an increased risk of developing molar pregnancies. Two genes have been identified: NLRP7 and KHDC3L (on chromosome 6), which are inherited in an autosomal recessive manner [35].

Discussion

GTN pathology can affect female body, causing more serious complications such as death. Although there are several methods to assess GTN grade, genetic factors are frequently ignored. That is why, in our systematic review article, we investigated the genetic alterations that influence the occurrence of GTN. The studies showed that altered gene expression, presence of gene mutations along with DNA methylation in 13 genes (maspin, MCL-1, COX4I1, GnT-IVa, ASPPI, SNRPN, MEST, c-erbB-2, mutant p53, NLRP7, KHDC3L, MTHFR C677T) can lead to GTN occurrence. Investigations also showed that the presence of Mutant p53, NLRP7, and KHDC3L can be effective in GTN stratification.

Maspin shows altered expression in various neoplasms and malignancies such as GTD [42]. GTDs, which include HMs and GTN, arise from abnormal proliferation of trophoblastic cells. Maspin, which is normally expressed in placental trophoblastic cells, has the potential to inhibit trophoblastic invasion. Studies show that maspin expression is decreased in GTD, especially in cases progressing to GTN, suggesting its potential prognostic significance [13]. Furthermore, studies show that the expression pattern of maspin and mutant p53 is associated with the development of GTN [16]. In contrast, MCL-1, an anti-apoptotic protein, is increased in GTD, which correlates with clinical outcomes. Fong et al. found a significant association between MCL-1 expression levels and GTD prognosis, suggesting its role in disease progression [18].

Furthermore, gestational exposure to environmental cadmium can induce placental apoptosis and fetal growth restriction through parkin-modulated degradation of MCL-1 [19]. COX4I1 regulates trophoblast cell proliferation, migration, and invasion by modulating mitochondrial function. Yu et al. demonstrated that COX4I1 influences trophoblast behavior, highlighting its importance in placental development and GTD [20]. GnT-IVa promotes the invasion of choriocarcinoma, a malignant form of GTN [21]. High GnT-IVa expression is associated with increased invasiveness of choriocarcinoma cells [22]. Downregulation of ASPP1 in GTD correlates with hypermethylation, decreased apoptotic activity, and clinical outcomes. Mak et al. found that downregulation of ASPP1 is associated with adverse clinical outcomes in GTD, suggesting its role in tumor suppression and apoptosis [23]. Epigenetic modifications in placental DMRs, including SNRPN and MEST, are subject to variation in normal pregnancy, pathological conditions, and folate supplementation. Rahat et al. demonstrated that aberrant epigenetic regulation of SNRPN and MEST may contribute to the development and progression of GTD [12], while c-erbB-2 is considered a prognostic marker in GTD. Ozbakir and Altintas suggested that MDM2 may serve as a prognostic marker in GTN, potentially complementing immunohistochemical tissue markers [25]. Hasanzadeh et al. examined the expression of p53 and c-erbB-2 in trophoblastic tissue, evaluating their prognostic value in diagnosing malignant progression of molar pregnancy [43]. Missaoui et al. performed immunohistochemical analysis of c-erbB-2, Bcl-2, p53, p21WAF1/Cip1, p63, and Ki-67 expression in HM. Mutant p53 showed altered expression patterns in GTD, correlating with GTN development [27]. Sun et al. demonstrated that maspin⁻ and m-p53⁺ expression was associated with GTN development in HMs [14]. However, Chen et al. found rare mutations in the tumor suppressor gene p53 in GTN [29]. NLRP7, a maternal-effect gene, is involved in recurrent RHM and GTN. Tao et al. identified novel pathogenic NLRP7 variations that increase the risk of GTN [30]. Kopelman and Hope reported a high-risk GTN case resulting from a homozygous NLRP7 mutation [28]. KHDC3L has shown pathogenic variations that increase the risk of developing GTN. Kocabey et al. highlighted the high risk of developing GTN in RHM with pathogenic variations in KHDC3L [44]. The MTHFR gene, involved in folate metabolism, has been investigated for its role in the treatment outcome of GTN. Patel et al. presented a case report highlighting the challenges associated with GTN treatment in patients with MTHFR mutations [38]. Lasecka et al. found that the 667C>T and 1298A>C polymorphisms of the MTHFR gene do not predict the response to methotrexate in patients with GTN [39]. Qu et al. suggested that the presence of the C677T polymorphism of the MTHFR gene in molar tissue predicts the failure of methotrexate treatment in low-risk GTN [40].

Key points of our review suggest that genetic alterations are recognized as major factors contributing to the onset of GTN, with alterations in gene expression, gene mutations, and DNA methylation patterns frequently observed in affected cases. Key genes implicated in the pathogenesis of GTN include maspin, MCL-1, COX4I1, GnT-IVa, ASPP1, SNRPN, MEST, c-erbB-2, mutant p53, NLRP7, KHDC3L, and MTHFR C677T. Among these, alterations or mutations in maspin, mutant p53, NLRP7, and KHDC3L play a particularly significant role in GTN risk stratification, supported by evidence linking NLRP7 and KHDC3L mutations to familial and recurrent molar pregnancies and demonstrating their impact on DNA methylation and genomic imprinting. Therefore, it is

recommended that physicians perform genetic profiling to facilitate stratification of patients with GTN into high- and low-risk groups, allowing for more accurate prognosis and treatment of the disease.

Limitations and suggestions for future research

Since this study is a systematic review and the availability of the English version was considered as an inclusion criterion, some data were probably excluded due to the lack of an English language version. On the other hand, the articles were published on a small statistical sample, which requires genetic research in a larger number of GTN cases. Therefore, it is recommended for future studies to use larger sample sizes and publish the study results preferably in English.

Conclusion

Interactions of various genes, including maspin, MCL-1, COX4I1, GnT-IVa, ASPP1, SNRPN, MEST, c-erbB-2, mutant p53, NLRP7, KHDC3L, and MTHFR, contribute to the development, progression, and treatment outcome of GTD. Further studies are needed to fully elucidate the role of these genes and their interactions in GTD, which may lead to improved diagnostic and therapeutic strategies.

Abbreviations

GTN: gestational trophoblastic neoplasia; β -hCG: beta-human chorionic gonadotropin; FIGO: International Federation of Gynecology and Obstetrics; WHO: World Health Organization; PSTT: placental site trophoblastic tumor; ETT: epithelioid trophoblastic tumor; MeSH: Medical Subject Headings; DMRs: differentially methylated regions; HMs: hydatidiform moles; COX4I1: cytochrome C oxidase subunit IV isoform 1; EVT: extravillous trophoblast; miRNA: microRNAs; GnT-IVa: N-acetylglucosaminyltransferase IVa; ASPPs: apoptosis-stimulating proteins of p53; SNRPN: small nuclear ribonucleoprotein polypeptide N; m-p53: mutant p53; MTHFR: methylenetetrahydrofolate reductase.

Author contributions

AEJ and ZV conceptualized and designed the study, supervised data collection, interpreted the results, and edited the manuscript. SNH and SAJ collected the data, prepared the tables, and wrote the Methods and Results sections. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and analyzed for this paper are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Supplement 1. Static data representing information from each study regarding gene alterations in GTN cases

First author	Year	Gene	Role in GTN	Gene alteration in GTN	Main findings	Type of GTN	Gene assessment assay
Fong PY.	2005	MCL-1	Gestational trophoblastic neoplasia (GTN) pathogenesis	MCL-1 expression correlates with clinical outcome	MCL-1 expression is associated with clinical outcome in GTD.	GTD	Differential expression study
Zhu HL.	2022	MCL-1	GTN pathogenesis	Parkin-modulated MCL-1 degradation	Environmental cadmium induces placental apoptosis and fetal growth restriction via parkin-modulated MCL-1 degradation	GTN	Not specified
Zhu HL.	2022	NLRP7	GTN pathogenesis	Mutation	Recurrent HM (RHM) with or without post-molar GTN can have a genetic cause (NLRP7 mutation) with an autosomal recessive pattern of inheritance.	Post-molar GTN	Not specified
Li HR.	2006	Maspin	GTN pathogenesis Involved in GTN risk stratification	Reduced expression	There is downregulated expression of maspin in gestational trophoblastic diseases, and the downregulation is more prominent in HMs.	HMs, CC, placental site trophoblastic tumor	Immunohistochemical staining, RT-PCR
Sun P.	2016	Maspin m-p53	GTN pathogenesis Involved in GTN risk stratification	Maspin levels were reduced m-p53 levels were increased	Maspin ⁺ and m-p53 ⁺ expression is associated with the development of GTN in HMs. Low-risk group exhibited a higher rate of maspin ⁺ expression. m-p53 expression was significantly higher at advanced stages	HMs and invasive moles or CC	Immunohistochemistry
Onalan G.	2021	Maspin	GTN pathogenesis Involved in GTN risk stratification	Maspin expression levels in placentas of preeclampsia patients > than in placentas of intrauterine growth restriction patients	Maspin expression may be used to distinguish between preeclampsia and intrauterine growth restriction 11 times higher in preeclampsia patients	Preeclampsia and intrauterine growth restriction	Not specified
Yu J.	2024	COX4-1	GTN pathogenesis	The gene regulates proliferation, migration, and invasion of trophoblast cells Expression of COX4-1, along with COX42, may be regulated by oxygen levels Reduced oxygen levels lead to increased COX4-2 expression and COX4-1 degradation	COX4-1 regulates proliferation, migration, and invasion of trophoblast cells via modulating mitochondrial function	GTN	Not specified
Nishino	2017	GnT-IVa	GTN pathogenesis	Promotes invasion	GnT-IVa promotes invasion of CC.	CC	Not specified
Niimi	2012	GnT-IVa	GTN pathogenesis	High expression promotes invasion	High expression of GnT-IVa promotes invasion of CC	CC	Not specified
Mak VC.	2011	ASPP1	GTN pathogenesis	Downregulation in GTD	Downregulation correlated with clinical outcome Correlation with hypermethylation and apoptotic activity	Gestational trophoblastic disease	Not specified
Rahat B.	2017	SNRPN	GTN pathogenesis	Variations in epigenetic modifications	Epigenetic modifications were subject to variations. Variations in normal gestation, pathological conditions, and folate supplementation	GTN	Not specified
Rahat B.	2017	MEST	GTN pathogenesis	Variations in epigenetic modifications	Epigenetic modifications were subject to variations Variations in normal gestation, pathological conditions, and folate supplementation.	GTN	Not specified
Ozbakir B.	2023	c-erbB-2	GTN pathogenesis	Significantly elevated in GTN	c-erbB-2 positivity was higher in GTN group compared with the HM in complete remission group	GTN	Immunohistochemistry
Hasanzadeh M.	2016	c-erbB-2	GTN pathogenesis	Overexpression in GTN	High expression of c-erbB-2 in trophoblastic cells could predict GTN during the early stages Cutoff value of 12.5% for percentage of cytotrophoblast with c-erbB-2 membranous staining	Molar pregnancy progressing to GTN	Immunohistochemistry
Missaoui N.	2019	c-erbB-2	GTN pathogenesis	N/A	N/A	HM	Immunohistochemical analysis
Sun P.	2016	M-p53	GTN pathogenesis Involved in GTN risk stratification	N/A	Expression patterns of mutant p53 are associated with the development of GTN	GTN	Not specified
Chen CA.	1994	p53	GTN pathogenesis	N/A	Infrequent mutation in tumor suppressor gene p53 in GTN	GTN	Not specified
Hasanzadeh M.	2016	p53	GTN pathogenesis	Overexpression in GTN	High expression of p53 in trophoblastic cells could predict GTN during the early stages Cutoff values for percentage of p53 ⁺ immunostained	Molar pregnancy progressing to	Immunohistochemistry

First author	Year	Gene	Role in GTN	Gene alteration in GTN	Main findings	Type of GTN	Gene assessment assay
					cytotrophoblast and syncytiotrophoblast were 5.5% and 2.5%, respectively	GTN	
Kopelman ZA.	2021	NLRP7	GTN pathogenesis Involved in GTN risk stratification	Homozygous mutation	First reported case of a patient with a homozygous NLRP7 mutation and subsequent high-risk GTN	High-risk GTN	Germline testing
Tao C.	2023	NLRP7	GTN pathogenesis Involved in GTN risk stratification	Novo pathogenic variations	NLRP7 mutations increase the risk of GTN	GTN	Not specified
Zhang P.	Not specified	NLRP7	GTN pathogenesis Involved in GTN risk stratification	Single rare heterozygous variants	Associations with single rare heterozygous NLRP7 variants for Chinese patients with sporadic gestational trophoblastic diseases	Gestational Trophoblastic Diseases	Not specified
Abi Nahed R.	2022	NLRP7	GTN pathogenesis Involved in GTN risk stratification	Overexpressed in choriocarcinoma (CC) trophoblast cells	NLRP7 may contribute to the acquisition of immune tolerance	Choriocarcinoma	Not specified
Alici-Garipcan A.	2020	NLRP7	GTN pathogenesis Involved in GTN risk stratification	Reduced expression in hydatidiform mole (HM) cells	Impaired NLRP7 expression results in precocious pluripotency factors, activation of trophoblast lineage markers, and promotes maturation of differentiated extraembryonic cell types, with 88% loss of expression	Complete HM	Whole transcriptome profiling
Reynaud D.	2023	NLRP7	GTN pathogenesis Involved in GTN risk stratification	Not specified	NLRP7 enhances CC cell survival disruption of NLRP7 expression leads to premature development of pluripotency factors, activation of trophoblastic lineage markers, and promotes maturation of differentiated extraembryonic cell types. The loss of expression is 88%. NLRP7 increases the survival of CC cells	CC	Not specified
Patel JM.	2023	MTHFR	GTN pathogenesis	MTHFR C677T mutation	MTHFR mutation led to an alteration of recommended chemotherapy regimen; the patient was counseled regarding reduced efficacy and increased toxicity of methotrexate therapy and opted for ActD regimen	Post-molar GTN	Not specified
Lasecka L.	2011	MTHFR	GTN pathogenesis	667C>T and 1298A>C polymorphisms	667C>T and 1298A>C polymorphisms of MTHFR do not predict response to methotrexate in patients with GTN	GTN	Not specified
Qu J.	2017	MTHFR	GTN pathogenesis	MTHFR C677T polymorphism	Presence of the methylenetetrahydrofolate reductase gene polymorphism MTHFR C677T in molar tissue but not maternal blood predicts failure of methotrexate treatment for low-risk GTN	Low-risk GTN	Not specified
Rezaei M.	2016	KHDC3L	GTN pathogenesis Involved in GTN risk stratification	Two novel protein-truncating mutations in a homozygous state	Two additional mutations provide further evidence for the important role of KHDC3L in the pathophysiology of RHM and increase the diversity of mutations described in Asian populations c.17_20delGGTT in Iranian patient and a splice mutation, c.349+1G>A, in the Indian patient	RHM	KHDC3L sequencing
Fallahi J.	2020	KHDC3L	GTN pathogenesis Involved in GTN risk stratification	c.1A>G mutation	The c.1A>G mutation in the KHDC3L gene is the most common mutation in the world, and also the presence of a founder effect for this particular mutation in Iranian populations c.1A>G is the most common mutation in the KHDC3L gene to date, and also the first report of a homozygous condition that resulted in RHM	RHM	Sanger sequencing

MCL-1, myeloid cell leukemia 1; NLRP7, NLR family pyrin domain containing 7; maspin, mammary serine protease inhibitor; m-p53, mutant p53; COX4-1, cytochrome c oxidase subunit 4 isoform 1; GnT-IVa, N-acetylglucosaminyltransferase IVa; ASP1, apoptosis-stimulating protein p53-1; SNRPN, small nuclear ribonucleoprotein polypeptide N; MEST, mesoderm-specific transcript; MTHFR, methylenetetrahydrofolate reductase; KHDC3L, KH domain-containing protein 3-like; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; HM, hydatidiform mole.