Supplementary table 1: Details of the included studies

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Author | Year | Type of study | Sample size | Main finding | Reference number |
| 1 | Al-Jabri et al. | 2023 | Cross-sectional | 95 PHM142 CHM | Significantly lower BCL-2 expression in CHM compared to PHM | [66] |
| 2 | Jahanbin et al. | 2023 | Cross-sectional | 40 PHM47 CHM | Significantly higher expression of Twist-1 in villous stromal cells of CHM compared to PHM | [88] |
| 3 | Hadi et al. | 2022 | Cross-sectional | 32 PHM 24 CHM 4 IM2 CC | Expression of p53 was significantly associated with IM and CC (p < 0.001) | [85] |
| 4 | Zainal et al. | 2021 | Cross-sectional | 41 PHM39 CHM2 Unclassified HM | Discordance between routine H&E and p57kip2 IHC of 33.0% | [28] |
| 5 | Ndukwe et al. | 2021 | Cross-sectional | 33 PHM21 CHM | Discordance between routine H&E diagnosis and p57kip2 IHC staining in 8 cases | [23] |
| 6 | Hoeijmakers et al. | 2021 | Case-control | 16 CHM with spontaneous regression16 CHM with progress to post-molar GTN | The density of NKT-like cells was significantly higher in patients with spontaneous regression compared to those who progressed to GTN (483 ± 296 vs. 295 ± 143, mean ± SD, p = 0.03). | [82] |
| 7 | Rezaei et al. | 2021 | Case series | 9 patients with RHM | Seven functional variants in a recessive state associated with RHM:Five variants in NLRP7One variant each in NLRP5 and PADI6 | [58] |
| 8 | Xing et al. | 2021 | Cross-sectional | 2,217 cases, including 2,160 uterine and 57 ectopic specimens. | CHMs were predominantly p57-negative (99.8%) and genotypically androgenetic (96.7%).PHMs showed predominant p57-positive expression (99%) and genotypically were mostly diandric triploid (97%). | [25] |
| 9 | Lin et al. | 2021 | Prospective Cohort | 39 complete moles | Identification of a distinct microRNA profile (miR-181b-5p and miR-181d-5p) associated with complete moles progressing to gestational trophoblastic neoplasia. | [69] |
| 10 | Alici-Garipcan et al. | 2020 | Experimental in vitro | Human skin samples collected from a HM patient with impaired NLRP7 expression and a healthy volunteer | Impaired NLRP7 expression results in downregulationof pluripotency factors, activation of trophoblast lineage markers, and maturation of the extraembryonic cell types.BMP pathway inhibition corrected the excessive trophoblast differentiation of patient-derivedPluripotent stem cells |  |
| 11 | Zhang et al. | 2020 | Experimental in vitro | 12 patients with NLRP7 NSVs  | NLRP7 NSVs affect the processing and secretion of IL-1β in patients with RHM. | [56] |
| 12 | Fallahi et al. | 2020 | Case report | 1 patient with history of 5 HM | Identification of a homozygous mutation (p.M1V, c.1A > G) in the KHDC3L gene in the patient with RHM | [50] |
| 13 | Fallahi et al. | 2020 | Case series | 14 Iranian patients with history of RHM | Identification of a specific mutation (c.1A>G) in the KHDC3L gene in patients with RHM | [49] |
| 14 | Zheng et al. | 2020 | Prospective Cohort | 165 CHM:138 homozygous27 heterozygous | Heterozygous/dispermic complete moles are clinically more aggressive and have a significantly higher risk for developing post-molar GTD compared to homozygous/monospermic CHM (p = 0.0009) | [16] |
| 15 | Hasan et al. | 2019 | Cross-sectional | 30 HA 30 PHM 30 CHM  | Significantly higher Ki-67 expression in cytotrophoblasts in CHM than PHM than HASignificantly higher Ki-67 expression in stromal cells in molar pregnancy than HA | [78] |
| 16 | Shalabi et al. | 2019 | Case report | 40-year-old Egyptian woman with RHM and CC | Two mutations identified in NLRP7 c.1358T>G, c.2655dupC | [52] |
| 17 | Kar et al. | 2019 | Prospective case control | 48 GTD8 HA40 normal placentas | Cyclin E and Ki-67 showed stronger staining intensity in CHM, CC, and PSTT. | [93] |
| 18 | Khooei et al. | 2019 | Case-control | 10 HA 8 PHM 11 CHM  | Significantly higher p53 expression in HM compared to HA | [84] |
| 19 | Missaoui et al. | 2019 | Case control | 39 HA 41 PHM 140 CHM  | Increased expression of BCL-2 in CHM and PHM compared to HA (p < 0.0001 and p = 0.001 respectively)Increased expression of ki-67 in CHM compared to PHM and HA (p = 0.005)Increased expression of p53 in CHM compared to PHM and HA (p < 0.0001)Increased expression of p63 in CHM and PHM compared to HA (p = 0.0001 and p = 0.001 respectively) | [70] |
| 20 | Khooei et al. | 2019 | Case-control | 10 HA 8 PHM 11 CHM  | Decreased expression of BCL-2 in CHM compared to PHM and HA | [68] |
| 21 | Takahashi et al. | 2019 | Experimental in vitro |  | Decreased or absent induction of p57KIP2 was associated with reduced sensitivity of TSmole cells to contact inhibition. | [27] |
| 22 | King et al. | 2019 | Case-control | 26 samples of CHM from 23 patients29 control | Abnormalities in epigenetic pathways were identified in CHMs, specifically in DNA methylation and imprinting patterns including downregulation of DNMT3A | [30] |
| 23 | Buza et al. | 2019 | Case series | 3 cases of HM | Paternal uniparental isodisomy of the tyrosine hydroxylase locus at chromosome 11p15.4 can lead to abnormal gestations that mimic hydatidiform mole both clinically and histologically. | [59] |
| 24 | Fallahi et al | 2019 | Case study | A woman with 5 RHM and her sister with miscarriage | A **novel mutation in the NLRP7 gene** (c.555\_557delCAC, p.Thr185del) was identified in homozygous state in the patient with recurrent molar pregnancies and a heterozygous state in her sister. | [53] |
| 25 | Ji et al | 2019 | Case-control | 5 HM5 control | **NLRP7 c.1441 G>A mutation was associated with biparental complete moles only.** | [46] |
| 26 | Guo et al. | 2019 | Case-control | 20 CHM15 control | Significantly lower expression of miRNA-196b in CHM compared to controlSignificantly higher expression of MP3K1 in CHM compared to control. | [79] |
| 27 | Chan et al. | 2019 | Observational/Experimental in vitro | 10 First trimester placentae11 Term placentae63 HM7 CC  | iASPP is overexpressed in HM and CC compared to normal placentaOverexpression of iASPP was associated with increased autophagy related protein expression while its silencing was associated with cellular senescence  | [76] |
| 28 | Cicek et al | 2018 | Case control | 8 PHM 8 CHM 8 control | IGF-1 expression is downregulated in CHM decidua and chorionic villi.LIF expression is downregulated in CHM decidua but upregulated in CHM trophoblasts. | [77] |
| 29 | Moussa et al | 2018 | Case-control | 16 HA 17 PHM 16 CHM  | Significantly decreased E-cadherin expression in HM compared to HASignificantly increased Ki-67 expression in PHM compared to HATwist-1 expression is significantly higher in CHM compared to PHM and HA | [75] |
| 30 | Nguyen et al. | 2018 | Case-control | MEI1 and REC114 werescreened in 99 affected women TOP6BL/C11orf80 wasscreened in 246 affected women | Identification of genetic mutations in MEI1, TOP6BL/C11orf80, and REC114associated with recurrent androgenetic CHM. |  [64] |
| 31 | Nguyen et al. | 2018 | Cross-sectional | 113 patients with RHM | Mutations in NLRP7 and KHDC3L were associated with diploid biparental HM, while recurrent molar pregnancies without mutations were associated mostly with diploid androgenic monospermic and triploid biparental dispermic | [48] |
| 32 | Chan et al. | 2018 | Cross-sectional | 49 HM | P53 mutations were identified: two missense mutations (p.R249S and p.R248Q) that disrupt p53 DNA binding sites, and a nonsense mutation (p.R213X) that prematurely truncates the protein, resulting in loss of function | [61] |
| 33 | Zhao et al. | 2018 | Experimental in vitro | Control 6 Regressed CHM 35 Post-CHM GTN 21  | miR-371a-5p and miR-518a-3p were upregulated in progressed CHMs (GTN)Functional analyses showed that miR-371a-5p and miR-518a-3p promoted proliferation, migration, and invasion of choriocarcinoma cells | [15] |
| 34 | Kubelka et al. | 2017 | Case series | 8 CHM | Absent expression of p57 in all CHM (both androgenetic diploidy and biparental diploidy) | [86] |
| 35 | Khashaba et al | 2017 | Cross-sectional | 11 PHM45 CHM | p57Kip2 IHC reclassified seven cases as CHM and one case as PHM. | [22] |
| 36 | Samadder et al. | 2017 | Cross- sectional | 23 CHM4 PHM1 unclassified HM25 controls | Negative immunostaining of p57Kip2 in 96% of CHM cases | [39] |
| 37 | Lelic et al. | 2017 | Cross-sectional | 12 CHM185 PHM1 unclassified HM | p57 immunostaining had 100 % concordance with pathohistological diagnoses in CHM group but 92% concordance in PHM group. | [23] |
| 38 | Kheradmand et al. | 2017 | Case-control | 20 PHM20 HA | Rate and intensity of stating was higher in PHM compared to HA (p = 0.027 and p < 0.001 respectively) | [83] |
| 39 | Wang et al | 2017 | Experimental in vitro | 16 HM20 normal placenta | miR-21 expression was significantly higher in HM tissues compared to control (p< 0.05).miR-21 inhibition significantly inhibited cell proliferation in choriocarcinoma cell lines (p <0.05), and overexpression promoted migration, and invasion in choriocarcinoma cell lines (p< 0.01 and < 0.05 respectively) | [81] |
| 40 | Sills et al. | 2017 | Case report | One patient with RHM and a homozygous pathogenic variant in NLRP7 (c.2810+2T > G) who underwent IVF | all embryos (total 10) from the patient arrested in development by 144 hours in culture.Karyomapping of the non-viable embryos revealed that all were diploid biparental. 8 embryos had variable aneuploidies. | [55] |
| 41 | Yu et al. | 2017 | Case-control | WES was done for 51 CHM patients and 47 healthy women. Candidate variants were analyzed in 199 CHM patients and 400 healthy controls | Two SNPs were associated with an increased risk of CHM (p < 0.05): c.G48C (p.Q16H) in the ERC1 gene and c.G1114A (p.G372S) in the KCNG4 gene | [60] |
| 42 | Triratanachat et al. | 2016 | Cross-sectional | 97 CHM30 PHM | P57KIP2 IHC results were discordant in 12 cases (9.4%) with the histopathological diagnosis. | [38] |
| 43 | Erol et al. | 2016 | Case-control | 17 HA 23 PHM 20 CHM  | Increased BCL-2 expression in HA compared to CHM and PHM (p < 0.001).Decreased CD117 staining percentage in HA compared to CHM and PHM (p < 0.001).Increased c-erB-2 expression in CHM compared to PHM and HA (p = 0.003)Absent expression of p57 in CHMNo significant difference between PHM and HA (p < 0.001) | [71] |
| 44 | Erol et al. | 2016 | Case-control | 23 HA 24 PHM 23 CHM  | Decreasing E-cadherin expression from HA to PHM to CHM (p < 0.001)Increased inhibin-alpha expression in molar pregnancy compared with HA (p < 0.001)Increased expression of p53 in CHM compared to PHM and HA (p < 0.001) | [14] |
| 45 | Hasanzadeh et al. | 2016 | Cross-sectional | 10 PHM 18 CHM 30 GTN  | Increased c-erB-2 expression in cytotrophoblasts in GTN compared to simple HM (p = 0.000).Increased expression of p53 in GTN compared to simple HM (p = 0.000). | [74] |
| 46 | Bolze et al. | 2016 | Case-control | 8 Control 6 PHM 12 CHM 1 IM 1 CC 1 PSTT  | the staining intensity of the Syncyntin-1 surface subunit C-terminus was significantly higher in HM, especially those with malignant transformation on follow up (p < 0.001) | [34] |
| 47 | Sun et al. | 2016 | Case control | Control 48 Regressed HM 49 Progressed HM 39  | Maspin was inversely correlated with FIGO prognostic score (p = 0.041) whereas expression of m-p53 was positively correlated with FIGO stage (p= 0.019). | [80] |
| 48 | Braga et al. | 2016 | Retrospective cohort | Regressed CHM 590Post-CHM GTN 190 | The NPV for GTN of apoptotic index (using Capase-3 IHC staining) ≥ 4.0% was 97%  | [72] |
| 49 | Wang et al. | 2016 | Case control | Control 36PHM 25 CHM 48IM 12 | Decreasing IMP3 expression from normal placental tissues, to PHM, to CHM, to IM (p < 0.05) | [73] |
| 50 | Hemida et al. | 2016 | Case report | Egyptian woman with FRHM | Sequencing of the NLPR7 gene in the patient revealed a homozygous base change in exon 2, c.197G>A, leading to a truncated protein p.W66∗. | [62] |
| 51 | Ito et al. | 2016 | Case series | four Japanese RHM cases | Whole-exome sequencing identified a homozygous nonsense mutation in the NLRP7 gene (c.584G>A; p.W195X) in one patient.Genotyping of molar tissues confirmed biparental origin in all four cases.There was a specific loss of maternal DNA methylation in DMRs of PEG3, SNRPN, and PEG10. | [63] |
| 52 | Rezaei et al. | 2016 | Case series | One Iranian patient and one Indian patient with RHM | Identified a homozygous 4-bp deletion mutation in KHDC3L (c.17-20delGGTT; p.Arg6Leufs∗7) in the Iranian patient and a homozygous splice mutation in KHDC3L (c.349+1G>A) in the Indian patient.No mutation in NLRP7 gene was found. | [51] |
| 53 | Reddy et al. | 2016 | Case series | 16 patients with RHM | 11 Novel NLRP7 variants were identified | [57] |
| 54 | Rahat et al. | 2016 | Cross sectional | 30 first trimester normal pregnancy30 second trimester normal pregnancy30 third trimester normal pregnancy30 pregnancy complicated with pre-eclampsia15 molar pregnancy | Development of choriocarcinoma was associated with DNA methylation and associated with lower expression of STAT5. | [37] |
| 55 | Luchini et al. | 2015 | Case control | 23 Abortions10 PHM 12 CHM 7 Term placentae | Expression of twist-1 is significantly higher in CHM compared to PHM (p < 0.05) and HA (p < 0.001) | [89] |
| 56 | Fock et al | 2015 | Case-control | 12 CHM 50 Healthy placentae5 healthy decidua | Trophoblasts with invasive characteristics have significantly increased expression of ERBB2 and ERBB3 | [99] |
| 57 | Wargasetia et al. | 2015 | Case control | 6 Control 11 PHM 11 CHM 11 IM 9 CC  | Decreasing BCL-2 expression from PHM, to CHM, to invasive mole, to choriocarcinoma compared to normal placenta (p< 0.002)Increased Beclin-1 expression in choriocarcinoma (p < 0.05) | [67] |
| 58 | Pasdar et al | 2015 | descriptive observational study | 20 HM20 non-molar pregnancies | CHM: 9 out of 10 cases analyzed were diploid, and 1 case was tetraploid.PHM: 8 out of 10 cases analyzed were triploid, and 2 cases were diploid.Spontaneous Abortions: All 20 were diploid. | [20] |
| 59 | Masood et al. | 2015 | Case control | HA 30PHM 30CHM 30 | Increased intensity of p63 staining in HM compared to HA (p < 0.001) | [87] |
| 60 | Sasaki | 2014 | Retrospective observational | 14 equivocal cases were stained with p57kip2 and staining compared to stained sections of DNA established androgenetic CHM, triploid PHM and biparental abortions | p57kip2 IHC successfully differentiated CHM (negative staining) from PHM or HA (positive staining) in all 14 cases. | [24] |
| 61 | Sanchez et al. | 2015 | Cross sectional | 4 androgenetic moles5 RHM with NLRP7 mutation | Lack of methylation at maternal DMRs, might be associated with the development of RHM in patients with NLRP7 mutations. | [33] |
| 62 | Lertkhachonsuk et al. | 2015 | Observational/Cohort | Compared LINE-1 Methylation in:12 control38 HM19 GTNFor the longitudinal study: 145 hydatidifo-rm mole patients | Significant increase in unmethylated LINE-1 loci in the malignant trophoblast group compared to hydatidiform moles.Lower level of partially methylated LINE-1 loci and partially unmethylated LINE-1 loci were associated with a higher risk of developing postmolar GTN.When methylation level is combined with pretreatment β-hCG levels, the predictive accuracy for GTN, has a PPV of 77.4% and a NPV of 83.8% | [36] |
| 63 | Zheng et al. | 2014 | Cross sectional | 146 cases of suspected or diagnosed molar pregnancies underwent STR DNA genotyping | 95 cases classified as CHM (92 monospermic and 3 dispermic)34 cases classified as PHM (32 dispermic and 2 monospermic)17 cases classified as balanced biallelic gestations. | [28] |
| 64 | Banet et al. | 2014 | Cross sectional | 201 CHM158 PHM272 non-molar14 androgenetic/biparental mosaics. | 199 cases of complete moles were p57-negative. 1 was non-reactive and 1 was p57 positive androgenetic with retained maternalcopy of chromosome 11156 of PHM were p57-positive. And 2 PHM were p57-negative due to loss of maternal copy of chromosome 11.Non-molar specimens included 259 p57-positive biparental diploid cases, 9 p57-positive digynic triploid cases, and 2 p57-negative biparental diploid cases without morphological features of biparental hydatidiform mole and an uncertain etiology for loss of p57 expression. | [29] |
| 65 | Mahadevan et al. | 2014 | Experimental in vitro | Human Embryonic Stem Cells  | NLRP7 interacts with YY1, an importantchromatin-binding factor and can alter DNA methylation affecting trophoblast differentiation. | [32] |

PHM= Partial hydatidiform mole, CHM= Complete hydatidiform mole, BCL-2= B cell lymphoma-2, IM= Invasive mole, CC= Choriocarcinoma, HM= Hydatidiform mole, H&E= Hematoxylin and eosin, IHC= Immunohistochemistry, GTN= Gestational trophoblastic neoplasia, NKT-like cells= Natural Killer T-like Cells, SD= Standard deviation, RHM= Recurrent hydatidiform mole, NLRP7= NLR family pyrin domain containing 7, NLRP5= NLR family pyrin domain containing 5, PADI6= Peptidylarginine deiminase 6, BMP= Bone Morphogenetic Protein, NSVs= Non synonymous variants, IL-1β= interleukin-1β, KHDC3L= KH Domain Containing 3 Like, HA= Hydropic abortion, GTD= Gestational trophoblastic disease, PSTT= Placental site trophoblastic tumor, TSmole cells= Trophoblast stem cells from hydatidiform moles, DNMT3A= DNA methyltransferase 3 alpha enzyme, iASPP= inhibitor of apoptosis-stimulating protein of p53, IGF-1= Insulin like growth factor-1, LIF= leukemia inhibitory factor, IVF= In vitro fertilization, WES= Whole-exome sequencing, SNPs= single nucleotide polymorphisms, KCNG4= potassium voltage-gated channel modifier subfamily G member 4, FIGO= International Federation of Gynecology and Obstetrics, NPV= Negative predictive value, Apoptotic index = Positive caspase -3 staining cells / negative caspase-3 staining cells x 100, IMP3= insulin-like growth factor II mRNA-binding protein 3, FRHM= Familial recurrent hydatidiform mole, DMRs= differentially methylated regions, PEG3 = Paternally Expressed Gene 3, SNRPN = Small Nuclear Ribonucleoprotein Polypeptide N, PEG10 = Paternally Expressed Gene 10, STAT5= Signal Transducer and Activator of Transcription 5, ERBB2 = Receptor Tyrosine-Protein Kinase erbB-2, ERBB3 = Receptor Tyrosine-Protein Kinase erbB-3, LINE-1= Long Interspersed Nuclear Element-1, β-hCG= beta human chorionic gonadotropin, PPV= Positive predictive value, STR= Short tandem repeat, YY1= Yin Yang 1

Bottom of Form