Supplementary table 1: Details of the included studies

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|  | Author | Year | Type of study | Sample size | Main finding | Reference number |
| 1 | Al-Jabri et al. | 2023 | Cross-sectional | 95 PHM  142 CHM | Significantly lower BCL-2 expression in CHM compared to PHM | [66] |
| 2 | Jahanbin et al. | 2023 | Cross-sectional | 40 PHM  47 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 IM  2 CC | Expression of p53 was significantly associated with IM and CC (p < 0.001) | [85] |
| 4 | Zainal et al. | 2021 | Cross-sectional | 41 PHM  39 CHM  2 Unclassified HM | Discordance between routine H&E and p57kip2 IHC of 33.0% | [28] |
| 5 | Ndukwe et al. | 2021 | Cross-sectional | 33 PHM  21 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 regression  16 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 NLRP7  One 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 downregulation  of pluripotency factors, activation of trophoblast lineage markers, and maturation of the extraembryonic cell types.  BMP pathway inhibition corrected the excessive trophoblast differentiation of patient-derived  Pluripotent 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 homozygous  27 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 HA  Significantly 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 GTD  8 HA  40 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 patients  29 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 HM  5 control | **NLRP7 c.1441 G>A mutation was associated with biparental complete moles only.** | [46] |
| 26 | Guo et al. | 2019 | Case-control | 20 CHM  15 control | Significantly lower expression of miRNA-196b in CHM compared to control  Significantly higher expression of MP3K1 in CHM compared to control. | [79] |
| 27 | Chan et al. | 2019 | Observational/Experimental in vitro | 10 First trimester placentae  11 Term placentae  63 HM  7 CC | iASPP is overexpressed in HM and CC compared to normal placenta  Overexpression 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 HA  Significantly increased Ki-67 expression in PHM compared to HA  Twist-1 expression is significantly higher in CHM compared to PHM and HA | [75] |
| 30 | Nguyen et al. | 2018 | Case-control | MEI1 and REC114 were  screened in 99 affected women  TOP6BL/C11orf80 was  screened in 246 affected women | Identification of genetic mutations in MEI1, TOP6BL/C11orf80, and REC114  associated 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 PHM  45 CHM | p57Kip2 IHC reclassified seven cases as CHM and one case as PHM. | [22] |
| 36 | Samadder et al. | 2017 | Cross- sectional | 23 CHM  4 PHM  1 unclassified HM  25 controls | Negative immunostaining of p57Kip2 in 96% of CHM cases | [39] |
| 37 | Lelic et al. | 2017 | Cross-sectional | 12 CHM  185 PHM  1 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 PHM  20 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 HM  20 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 CHM  30 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 CHM  No 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 590  Post-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 36  PHM 25  CHM 48  IM 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 pregnancy  30 second trimester normal pregnancy  30 third trimester normal pregnancy  30 pregnancy complicated with pre-eclampsia  15 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 Abortions  10 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 placentae  5 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 HM  20 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 30  PHM 30  CHM 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 moles  5 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 control  38 HM  19 GTN  For 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 CHM  158 PHM  272 non-molar  14 androgenetic/biparental mosaics. | 199 cases of complete moles were p57-negative. 1 was non-reactive and 1 was p57 positive androgenetic with retained maternal  copy of chromosome 11  156 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 important  chromatin-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

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