**Supporting Information**

Systematic review of preterm birth multi-omic biomarker studies

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Table S1. Targeted preterm birth genomics biomarker studies. Maternal genes/SNPs biomarkers identified in the literature (n=30).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Ethnic groups | Genes/SNPs identified | Phenotype | Total number of maternal participants | Technology/  technique | P value |
| [Pandey et al. (2020)](#_ENREF_114)  (Ref. 1) | Indian | *MMP-1*\_rs1799750  *MMP8*\_rs11225395  *IL-6\_*rs1800795  *MMP-8\_*rs2155052  *MMP-9\_*rs3918242 | PTB (<37 weeks) | 510  [PTB n=255, control n=255] | Restriction Fragment length polymorphism | NA |
| [Hao et al. (2020)](#_ENREF_55) (Ref. 2) | Chinese | *SOD2* (rs2758352), *SOD3* (rs699473), and *CAT* (rs769214) | SPTB (<37 weeks) | 528  [PTB n =147, control n=381] | MALDI-TOF MS (MassArray, Sequenom) | P < 0.01 |
| [Gillespie et al. (2017)](#_ENREF_47) (Ref. 3) | African American (non-Hispanic) | GG genotype of *IL1RN* SNP rs2637988 | Birth timing (28–32 weeks) | 89 | TaqMan SNP Genotyping Assays | P=0.04 |
| [Frey et al. (2016)](#_ENREF_42) (Ref. 4) | African American | **Alleles sPTB vs Control deliveries:**  *PRKCA* (rs7225452, rs4486944, rs6504424, rs16960070)  *FLT1* (rs12428494)  **Genotypes sPTB <37 weeks:**  *MMP2* (rs11639960)  *TIMP2* (rs2277698)  *IL16* (rs7171517)  *PRKCA* (rs16960070, rs7225452, rs6504424, rs4486944)  **sPTB before <34 weeks:**  *MMP1* (rs7945189)  *MMP2* (rs11639960)  *LIFR-AS1* (rs6451398) | sPTB  (<37 weeks and <34 weeks) | 833 | Customized 1536 SNP Illumina Golden Gate genotyping array | Findings reported: p<7.4x10-5 |
| [Langmia et al. (2016)](#_ENREF_83) (Ref. 5) | Malays, Chinese or Indians | *IL1R2* rs2072476 | PTB  (24-36 weeks) | 664 | MALDI-TOF MS (MassArray, Sequenom) | p=0.017 |
| [Ramos et al. (2016)](#_ENREF_130)  (Ref. 6) | Brazilian population:  European, Amerindian and African ancestries | *IL10-1082G* (rs1800896) and *TLR2A* (rs4696480) alleles increased risk for PPROM  *TNFA-238A* (rs361525) - protective against PTL | PTL with intact membranes (<37 weeks), PPROM | 603  [PTL n=136, PPROM n=65, control n=402] | TaqMan SNP Genotyping Assays | P< 0.05 |
| [Bream et al. (2013)](#_ENREF_16) (Ref. 7) | American and Danish | *ENPP1*, *IGFBP3*, *DHCR7* and *TRAF2*. | PTB  (<37 weeks) | 37 | TaqMan | P<0.01 |
| [Falah et al. (2013)](#_ENREF_37) (Ref. 8) | Discovery cohort, USA: white, African-American, Finnish and Hispanic.    Replication cohort: Danish. | **SNPs in US white mothers:**  *IL23R* (rs11465804); *LPL* (rs12678919);  *CDKN2* (rs4977574); *MHC* (rs6457617);  *HLA-DRB1* (rs6457620); *HLA-DRA* (rs9268645); *HLA-DQA1* (rs9272346)  **US African-American mothers:**  *PCSK9* (rs11591147); *GCKR* (rs780094);  *FGB/FGA/FGG* (rs6056)  **US Hispanic mothers:**  *LDLR* (rs6511720)  **Danish, PTB protective association:**  *HLA-DQB1* (rs1063355) | PTB (<37 weeks) | Discovery cohort: 1,792  [sPTB n=673, control n=1,119]  Replication cohort: 2,000  [PTB n=1,000, control n=1,000] | MALDI-TOF MS (MassArray, Sequenom) | P<0.05 |
| [Harmon et al. (2013)](#_ENREF_56)  (Ref. 9) | European-American, African-American | **European:**  *IFNGR2* – strong association  *KIR3DL2* – strong association  *IL4* and *IL13* (rs3091307)  **European and African Americans:**  reduced risk of PTB - *IL12A* and *CSF2* | sPTB  (<37 weeks) | 1,646  [PTB n=347, control n=1299] | Illumina GoldenGate SNP assay | NA |
| [Iwanaga et al. (2011)](#_ENREF_65)  (Ref. 10) | Japanese | FcγRIIB-nt645 + 25AA carriers had a significantly shorter gestational period and a higher rate of PTB (periodontitis) | PTB  (<37 weeks) | 122  [PTB n=51, control n=71] | Big Dye Cycle Sequencing (Applied Biosystems) | p=0.032 |
| [Romero et al. (2010)](#_ENREF_134)  (Ref. 11) | Hispanic origin | **GWAS analysis:**  *TIMP2* (rs2277698)  **Global haplotype analysis**:  *COL4A3* (rs1882435-rs10178458-rs55997063) | sPTB  (<37 weeks) | 822  [PTB n=223, control n=599] | MALDI-TOF MS (MassArray, Sequenom) | P<0.01 |
| [Mustafa et al. (2010)](#_ENREF_107) (Ref. 12) | Indian | *GSTM1-/GSTT1-* (increased risk of PTL) | PTL  (<37 weeks) | 123  [PTB n=60, control n=63] | Multiplex PCR | p=0.028 |
| [Romero et al. (2010)](#_ENREF_132)  (Ref. 13) | Hispanic origin | *TIMP2* (rs2277698); *ANG* (rs11701); *TLR1* (rs3923647); *NOS3* (rs3730305); *COL4A3* (rs1882435); *PTGER1* (rs3745459) | PPROM  (PTB, 21-36 weeks) | 824  [pPROM n=225, control n= 599] | MALDI-TOF MS (MassArray, Sequenom) | P<0.01 |
| [Kwon et al. (2009)](#_ENREF_82) (Ref. 14) | Korea | *ICAM-1* K469E polymorphism | sPTB  (<37 weeks) | 206  [PTB n=53, control n=153] | PCR and auto-sequencing | P<0.05 |
| [Gebhardt et al. (2009)](#_ENREF_43)  (Ref. 15) | South African (Black, European and Asian ancestry) | *LGALS13b*  *TNFA* | PTB  (<37 weeks) | 450 | PCR | P<0.05 |
| [Menon et al. (2008)](#_ENREF_98) (Ref. 16) | African Americans and Caucasians | *TNF-α,* *TNFR1* and *TNFR2* | PTB  (<37 weeks) | 606  [PTB n=221, control n=385] | Illumina GoldenGate genotyping | P<0.05 |
| [Velez et al. (2008)](#_ENREF_159) (Ref. 17) | Caucasian | *CRHBP* (rs1875999, rs32897, rs10055255); *FV* (rs9332624); *IL5* (rs739718); *tPA* (rs879293); *PTGER3* (rs977214, rs594454); *SCNN1A/sTNF-R1* (rs3764874) | PTB  (<37 weeks) | 339  [PTB n=145, control n=194] | Illumina's GoldenGate genotyping | P<0.01 |
| [Steffen et al. (2007)](#_ENREF_148)  (Ref. 18) | All ethnic groups | **Gestational age:**  *ABCA1* (rs4149313), *APOE* (rs7412), *LCAT* (rs1109166), *LIPC* (rs6083)  **Prematurity (PTB):**  *DHCR24* (rs2274941) | Gestational age (22 to 36 weeks) and PTB | 351 | TaqMan chemistry | P<0.05 |
| [Ehn et al. (2007)](#_ENREF_29) (Ref. 19) | American | Progesterone receptor (PGR):  rs653752, rs503362, rs4754732, rs1942836, alu insertion | PTB  (<37 weeks) | 415 | TaqMan | P < 0.05 |
| [Menon et al. (2006)](#_ENREF_99) (Ref. 20) | European-American | *TNF-α, IL-6, IL-6R* | sPTB  (<36 weeks) | 422  [PTB n=101, control n=321] | TaqMan assay | P<0.001 |
| [Kalish et al. (2006)](#_ENREF_70) (Ref. 21) | American (mixed) | **PPROM alleles:**  *CD14\*T; CD14\*T; IL1RN\*2; CD14\*T; hsp70-2\*G* | PPROM and sPTB  (<37 weeks) | 110  [PPROM n=28, sPTB n=72, control n=10] | PCR | P<0.05 |
| [Kalish et al. (2005)](#_ENREF_69)  (Ref. 22) | American (mixed) | *TNFRSF6* (genotype)  *TNFRSF6\*G* (allele) | PPROM  (37 weeks) | 119  [PPROM n=33, SPTB n=9, control n=77] | PCR | P<0.05 |
| [Annells et al. (2004)](#_ENREF_4)  (Ref. 23) | European | **PTB:**  *IL10 −1082A/−819T/−592A*,  *TNF +488A/−238G/−308G*,  *IL4 −509C/C*,  *MBL2* codon 54Asp  **PPROM:**  *IL10 −1082G/−819C/−592C* | PTB (<29 weeks) and PPROM | 387  [PTB n=202, control n=185] | PCR | P<0.05 |
| [Hartel et al. (2004)](#_ENREF_57) (Ref. 24) | Caucasian | *IL6-174G* | PTB  (<37 weeks) | 747  [PTB n=466, control n=281] | PCR | P=0.018 |
| [Valdez et al. (2004)](#_ENREF_158)  (Ref. 25) | Mexican | **Control vs Preterm:**  *MTHFR C677T*  *ACE D* (allele)  **Preterm without infection:**  *MTHFR T* polymorphism  **Premature rupture of membranes:**  *ACE* *D* | PTB (22–36 weeks), PROM and infection | 253  [PTB n=89, control n=164] | PCR | P<0.05 |
| [Miller et al. (2015)](#_ENREF_101) (Ref. 26) | Black, Hispanic, White, Other | *β2AR* or *ADRB2* (rs1042713, rs1042714) | Cervix length and PTB (<37 weeks) | 439 | Sanger sequencing and electrophoresis | NA |
| [Schmid et al. (2010)](#_ENREF_142) (Ref. 27) | Austria | *CRHR2* G/A (rs2267717) | PTB  (<37 weeks) | 200  [PTB n=100, control n=100] | PCR | NA |
| [Uvuz et al. (2009)](#_ENREF_156) (Ref. 28) | Turkish | *FVL, FVC, FII, MTHFR C677T, MTHFR C1298T, ACE* | PTB  (28-36 weeks) | 100  [PTB n=50, control n=50] | Nanogen Microarray | NA |
| [Wang et al. (2017)](#_ENREF_163) (Ref. 29) | Taiwanese | *MBL2* | PTB  (<37 weeks) | 306  [PTB n=51, control n=255] | TaqMan | NA |
| [Fortunato et al. (2008)](#_ENREF_41)  (Ref. 30) | Black and White women of non-Hispanic origin | *IL-6* (rs1554606, rs1880243, rs1800795, rs1800796, rs1800797)  *IL-6R* (rs4845622, rs4845623, rs6687726)  *TNF-α* (rs769178, rs1799964, rs1800629, rs1800683, rs3179004)  *TNFR1* (rs740841, rs1860545, rs2302350, rs3764874, rs4149577)  *TNFR2* (rs474247, rs590368, rs616645, rs653667, rs976881, rs1061631, rs5746053) | sPTB  (<36 weeks) | 1195  [PTB n=448, control n=747] | TaqMan assay | NA |

MALDI-TOF MS = matrix-assisted laser desorption/ionization time of flight mass spectrometry; PPROM = preterm pre-labour rupture of membranes; PTB = preterm birth;

PTL = preterm labour; sPTB = spontaneous preterm birth

Table S2. Preterm birth targeted transcriptomics studies of maternal samples (n=6).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Transcripts Identified | Phenotype | Sample type | Total number of maternal participants | Technology/  technique | P value |
| Manuck et al. (2021)  (Ref. 31) | **Genes at < 34 weeks:**  TLR2; DUSP1; RUNX3; PPP3CA; B2M; TLR4; IL10RA; PREX1; CYC1  **Genes at < 37 weeks:**  TLR2; DUSP1; B2M; TLR4; PREX1; IL10RB; RUNX3; PPP3CA; CXCR3; DDAH2; IL10RA; HSP90AB1; NCF1; RNF7 | spontaneous PTB  (<37 weeks and <34 weeks) | Blood | 136  [PTB (n=68), control (n=68] | Custom NanoString mRNA panel | P < 0.05 |
| [Zhou et al. (2021)](#_ENREF_171) (Ref. 32) | LINC00870 and LINC00094 | sPTB  (<37 weeks) | Blood | 165  [sPTB (n = 51), control (n=114)] | Bioinfomatics analysis using public databases | P < 0.05 |
| [Zhou et al. (2020)](#_ENREF_172) (Ref. 33) | EBF1-based miRNA transcripts (*MIR4266, MIR1251, MIR601,*  *MIR3612*) | sPTB  (<37 weeks) | Blood | 157  [sPTB n=51, control n=106] | Bioinformatics tools used: miRWalk and STarMirDB | P ≤ 0.018 |
| [Awasthi and Pandey (2019)](#_ENREF_6)  (Ref. 34) | TLR4 mRNA (increased expression in cases) | PTB  (<37 weeks) | Blood | 1118  [PTB n=559, control n=559] | Real-time PCR | P<0.001 |
| [Mustafa et al. (2015)](#_ENREF_106)  (Ref. 35) | COX-2 (increase fold change)  MnSOD and CAT (decreased fold change) | sPTB  (<37 weeks) | Blood | 100  [sPTB n=50, control n=50] | RT-PCR | P < 0.05 |
| [Lee et al. (2011)](#_ENREF_85) (Ref. 36) | IL-6R | PPROM and PTL (<37 weeks) | Amniotic fluid | 301  [Of which: PTL n=131, PPROM n=91] | Quantitative real-time RT-PCR | P < 0.01 |

PPROM = preterm pre-labour rupture of membranes; PTB = preterm birth; PTL = preterm labour; sPTB = spontaneous preterm birth

Table S3. Summary of 70 preterm birth targeted proteomics biomarker studies identified in a systematic search using PubMed, Web of Science and Science Direct. Multiple research studies targeted same or similar proteins.

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Protein | Gene symbol | UniProt ID |
| Afzal et al. (2017) (Ref. 37) | C-reactive protein | CRP | P02741 |
| Bakalis et al. (2012) (Ref. 38) | C-reactive protein | CRP | P02741 |
| Berkowitz et al. (1996) (Ref. 39) | Corticotropin-releasing hormone or factor (CRH, CRF or Corticoliberin) | CRH | P06850 |
| Bernstein et al. (1998) (Ref. 40) | Free beta-human chorionic gonadotropin (beta-hCG) fbhCG (Choriogonadotropin subunit beta 3) | CGB3 | P0DN86 |
| Beta et al. (2011)  (Ref. 41) | Alpha-fetoprotein (AFP) | AFP | P02771 |
| Biggio et al. (2005) (Ref. 42) | Matrix metalloproteinase-8 | MMP8 | P22894 |
| Cantonwine et al. (2016) (Ref. 43) | Apolipoprotein M (APOM) | APOM | O95445 |
|  | Inter-alpha-trypsin inhibitor heavy chain 4 (ITIH4) | ITIH4 | Q14624 |
|  | Kininogen-1 (KNG1) | KNG1 | P01042 |
|  | Phosphatidylcholine-sterol acyltransferase | LCAT | P04180 |
|  | Fibulin-1 | FBLN1 | P23142 |
|  | Inter-alpha-trypsin inhibitor heavy chain H2 | ITIH2 | P19823 |
|  | Alpha-1-antichymotrypsin | AACT | P01011 |
|  | Plasma kallikrein | KLKB1 | P03952 |
|  | Trypsin-3 | PRSS3 | P35030 |
|  | Coagulation factor XIII B chain | F13B | P05160 |
|  | Apolipoprotein L1 | APOL1 | O14791 |
|  | N-acetylmuramoyl-L-alanine amidase | PGRP2 | Q96PD5 |
|  | Thyroxine-binding globulin | SERPINA7 | P05543 |
|  | CD5 antigen-like | CD5L | O43866 |
|  | Carboxypeptidase N catalytic chain | CBPN | P15169 |
|  | Vitamin D-binding protein | VTDB | P02774 |
|  | Protein AMBP | AMBP | P02760 |
|  | Complement component C8 alpha chain | CO8A | P07357 |
|  | Inter-alpha-trypsin inhibitor heavy chain H1 | ITIH1 | P19827 |
|  | Transthyretin | TTR | P02766 |
|  | Coagulation factor XIII A chain | F13A1 | P00488 |
|  | Apolipoprotein A-I | APOA1 | P02647 |
|  | Magnesium transporter MRS2 homolog, mitochondrial | HPT | Q9HD23 |
| Catov et al. (2014) (Ref. 44) | nonesterified (free) fatty acids (NEFAs) \* |  |  |
| Curry et al. (2009) (Ref. 45) | Interleukin 2 (IL-2) | IL2 | P60568 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Tumour necrosis factor alpha (TNF-a) | TNF | P01375 |
|  | Interferon (IFN) gamma | IFNG | P63309 |
|  | Granulocyte colony-stimulating factor (GCSF) or macrophage (GM-CSF) | CSF2 | P04141 |
| Curry et al. (2007) (Ref. 46) | Interleukin 2 (IL-2) | IL2 | P60568 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Tumour necrosis factor alpha (TNF-a) | TNF | P01375 |
|  | Interferon (IFN) gamma | IFNG | P63309 |
|  | Granulocyte colony-stimulating factor (GCSF) or macrophage (GM-CSF) | CSF2 | P04141 |
| Dane et al. (2013) (Ref. 47) | Pregnancy associated plasma protein (PAPP-A or Pappalysin-1) | PAPPA | Q13219 |
|  | Free beta-human chorionic gonadotropin (beta-hCG) fbhCG (Choriogonadotropin subunit beta 3) | CGB3 | P0DN86 |
| Dunn et al. (2019) (Ref. 48) | Complement component C3 | C3 | P01024 |
|  | Complement factor B | CFB | P00751 |
| Ellis et al. (2002)  (Ref. 49) | Corticotropin-releasing hormone (CRH or Corticoliberin) | CRH | P06850 |
| Esplin et al. (2011) (Ref. 50) | Other peptides \* |  |  |
|  | Placental growth factor (PlGF) | PGF | P49763 |
|  | Corticotropin-releasing hormone (CRH or Corticoliberin) | CRH | P06850 |
|  | Ferritin | FTL | P02792 |
|  | Tumour necrosis factor alpha (TNF-a) | TNF | P01375 |
| Ferguson et al. (2014) (Ref. 51) | Interleukin 1 beta (IL-1β) | IL1B | P01584 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Interleukin 10 (IL-10) | IL10 | P22301 |
|  | Tumour necrosis factor alpha (TNF-a) | TNF | P01375 |
|  | C-reactive protein | CRP | P02741 |
| Forest et al. (1996) (Ref. 52) | Albumin | ALB | P02768 |
| Hallingstrom et al. (2020) (Ref. 53) | Adiponectin | ADIPOQ | Q15848 |
|  | Brain-derived neurotrophic factor | BDNF | P23560 |
|  | C-C motif chemokine 2 (monocyte chemotactic protein 1) | CCL2 or MCP1 | P13500 |
|  | C-C motif chemokine 3 (macrophage inflammatory protein 1-a (MIP-1-a)) | CCL3 | P10147 |
|  | C-C motif chemokine 5 | CCL5 | P13501 |
|  | C-reactive protein | CRP | P02741 |
|  | Granulocyte colony-stimulating factor (GCSF) or macrophage (GM-CSF) | CSF2 | P04141 |
|  | Insulin-like growth factor-binding protein 1 (IGFBP-1) | IGFBP1 | P08833 |
|  | Insulin-like growth factor-binding protein 3 (IGFBP-3) | IGFBP3 | P17936 |
|  | Interferon (IFN) gamma | IFNG | P63309 |
|  | Interleukin 1 beta (IL-1β) | IL1B | P01584 |
|  | Interleukin 10 (IL-10) | IL10 | P22301 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Interleukin 8 (IL-8) | CXCL8 | P10145 |
|  | interleukin-12A | IL12A | P29459 |
|  | Interleukin-17 | IL17 | Q5QEX9 |
|  | Interleukin-18 | IL-18 | Q9NQ49 |
|  | Leptin | LEP | P41159 |
|  | Macrophage migration inhibitory factor (MIF) | MIF | P14174 |
|  | Matrix metalloproteinase-9 | MMP9 | P14780 |
|  | Neurotrophin-3 | NTF3 | P20783 |
|  | Triggering receptor expressed on myeloid cells 1 | TREM1 | Q9NP99 |
|  | Tumour necrosis factor alpha (TNF-a) | TNF | P01375 |
|  | Tumour necrosis factor receptor 1 (TNFR1) | TNFR1 | P19438 |
| Hallingstrom et al. (2016) (Ref. 54) | C-reactive protein | CRP | P02741 |
|  | Triosephosphate isomerase | TPI1 | P60174 |
|  | Calcium-activated chloride channel regulator | CLCA1 | A8K7I4 |
|  | Malate dehydrogenase, cytoplasmic | MDH1 | P40925 |
|  | Cystatin-SN | CST1 | P01037 |
|  | Hemoglobin subunit delta | HBD | P02042 |
|  | Hemoglobin subunit alpha | HBA1 | P69905 |
|  | Hemoglobin subunit beta | HBB | P68871 |
|  | Glycodelin | PAEP | P09466 |
|  | Cathelicidin antimicrobial peptide | CAMP | P49913 |
| Holzman et al. (2001) (Ref. 55) | Corticotropin-releasing hormone (CRH or Corticoliberin) | CRH | P06850 |
| Holzman et al. (2013) (Ref. 56) | Corticotropin-releasing hormone (CRH or Corticoliberin) | CRH | P06850 |
|  | C-reactive protein | CRP | P02741 |
|  | Interleukin 1 beta (IL-1β) | IL1B | P01584 |
|  | Interleukin 2 (IL-2) | IL2 | P60568 |
|  | Interleukin-4 | IL4 | P05112 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | interleukin-12A | IL12A | P29459 |
|  | Interferon (IFN) gamma | IFNG | P63309 |
|  | Transforming growth factor beta-1 | TGFB1 | P01137 |
| Hudic et al. (2016) (Ref. 57) | Progesterone-Induced Blocking Factor | PIBF1 | Q8WXW3 |
| Hunter et al. (2016) (Ref. 58) | C-C motif chemokine 2 (CCL2) | CCL2 | P13500 |
|  | C-C motif chemokine 3 (CCL3) | CCL3 | P10147 |
|  | C-C motif chemokine 4 (CCL4) | CCL4 | P13236 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Interleukin 1 beta (IL-1β) | IL1B | P01584 |
|  | Interleukin 8 (IL-8) | CXCL8 | P10145 |
| Kaijomaa et al. (2016) (Ref. 59) | Pregnancy associated plasma protein (PAPP-A or Pappalysin-1) | PAPPA | Q13219 |
| Kalinka et al. (2005) (Ref. 60) | Interleukin-1 alpha | IL1A | P01583 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Interleukin 1 beta (IL-1β) | IL1B | P01584 |
|  | Interleukin 8 (IL-8) | CXCL8 | P10145 |
| Kallioniemi et al. (2013) (Ref. 61) | Insulin-like growth factor-binding protein 1 (IGFBP-1) | IGFBP1 | P08833 |
| Kansu-Celik et al. (2019) (Ref. 62) | Advanced glycation end products (AEGs) \* |  |  |
| Kesrouani et al. (2016) (Ref. 63) | C-reactive protein | CRP | P02741 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Matrix metalloproteinase-9 | MMP9 | P14780 |
| Kim et al. (2013)  (Ref. 64) | Vascular endothelial growth factor (VEGF) | VEGF | P15692 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Matrix metalloproteinase-8 | MMP8 | P22894 |
|  | C-reactive protein | CRP | P02741 |
| Kim et al. (2005)  (Ref. 65) | Free beta-human chorionic gonadotropin (beta-hCG) fbhCG (Choriogonadotropin subunit beta 3) | CGB3 | P0DN86 |
| Kirkegaard et al. (2011) (Ref. 66) | Free beta-human chorionic gonadotropin (beta-hCG) fbhCG (Choriogonadotropin subunit beta 3) | CGB3 | P0DN86 |
|  | Pregnancy associated plasma protein (PAPP-A or Pappalysin-1) | PAPPA | Q13219 |
| Kirkegaard et al. (2010) (Ref. 67) | Free beta-human chorionic gonadotropin (beta-hCG) fbhCG (Choriogonadotropin subunit beta 3) | CGB3 | P0DN86 |
|  | Pregnancy associated plasma protein (PAPP-A or Pappalysin-1) | PAPPA | Q13219 |
| Kramer et al. (2010) (Ref. 68) | C-reactive protein | CRP | P02741 |
|  | Interleukin 1 beta (IL-1β) | IL1B | P01584 |
|  | Interleukin 10 (IL-10) | IL10 | P22301 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Interleukin 8 (IL-8) | CXCL8 | P10145 |
|  | interleukin-12A | IL12A | P29459 |
|  | Interleukin-17 | IL17 | Q5QEX9 |
|  | Interleukin-18 | IL-18 | Q9NQ49 |
|  | Interleukin-4 | IL4 | P05112 |
|  | Matrix metalloproteinase-9 | MMP9 | P14780 |
|  | Interleukin-5 | IL5 | P05113 |
|  | Macrophage migration inhibitory factor (MIF) | MIF | P14174 |
|  | Matrix metalloproteinase-9 | MMP9 | P14780 |
|  | Triggering receptor expressed on myeloid cells 1 | TREM1 | Q9NP99 |
|  | C-C motif chemokine 3 (macrophage inflammatory protein 1-a (MIP-1-a)) | CCL3 | P10147 |
|  | Interferon (IFN) gamma | IFNG | P63309 |
|  | Transforming growth factor beta-1 | TGFB | P01137 |
|  | C-C motif chemokine 4 | CCL4 or MIP1B | P13236 |
|  | Brain-derived neurotrophic factor | BDNF | P23560 |
|  | Neurotrophin-3 | NTF3 | P20783 |
|  | Neurotrophin-4 | NTF4 | P34130 |
|  | Granulocyte colony-stimulating factor (GCSF) or macrophage (GM-CSF) | CSF2 | P04141 |
| Kumar et al. (2015) (Ref. 69) | Lipocalin-type prostaglandin D2 synthase (L-PGDS) | PTGDS | P41222 |
| Lee et al. (2016)  (Ref. 70) | Vascular endothelial growth factor (VEGF) | VEGF | P15692 |
|  | Placental growth factor (PlGF) | PGF | P49763 |
|  | Vascular endothelial growth factor receptor 1 | FLT1 | P17948 |
| Malamitsi-Puchner et al. (2006) (Ref. 71) | Intercellular adhesion molecule-1 (sICAM-1) | sICAM-1 | Q99930 |
|  | Vascular cell adhesion molecule | VCAM1 | P19320 |
|  | Neutrophil elastase | ELANE | P08246 |
|  | Secretory leukocyte proteinase inhibitor (SLPI) | SLPI | P03973 |
| Manning et al. (2019) (Ref. 72) | Interleukin 8 (IL-8) | CXCL8 | P10145 |
|  | Interleukin 1 beta (IL-1β) | IL1B | P01584 |
|  | Elafin | PI3 | P19957 |
|  | Beta-defensin 1 | HBD1 | P60022 |
|  | Granulocyte colony-stimulating factor (GCSF) or macrophage (GM-CSF) | CSF2 | P04141 |
|  | C-C motif chemokine 2 (monocyte chemotactic protein 1) | CCL2 or MCP1 | P13500 |
|  | Interleukin 10 (IL-10) | IL10 | P22301 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Interleukin-4 | IL4 | P05112 |
|  | interleukin-12A | IL12A | P29459 |
| Massaro et al. (2009) (Ref. 73) | Interleukin 6 (IL-6) | IL6 | P05231 |
| McDonald et al. (2015) (Ref. 74) | Complement component 5a (C5a) | C5 | P01031 |
|  | Vascular endothelial growth factor receptor 1 | FLT1 | P17948 |
|  | Intercellular adhesion molecule-1 (sICAM-1) | sICAM-1 | Q99930 |
|  | Interleukin-18-binding protein | IL18BP | O95998 |
|  | Chitinase-3-like protein 1 (CHI3L1) | CHI3L2 | P36222 |
|  | Endoglin | ENG | P17813 |
|  | Angiopoietin-related protein 3 (AngptL3) | ANGPTL3 | Q9Y5C1 |
| McElrath et al. (2019) (Ref. 75) | Inter-alpha-trypsin inhibitor heavy chain 4 (ITIH4) | ITIH4 | Q14624 |
|  | Inter-alpha-trypsin inhibitor heavy chain H2 | ITIH2 | P19823 |
|  | Phosphatidylcholine-sterol acyltransferase | LCAT | P04180 |
|  | Serotransferrin | TF | P02787 |
|  | Fibulin-1 | FBLN1 | P23142 |
| Mijal et al. (2012) (Ref. 76) | Vascular endothelial growth factor receptor 1 | FLT1 | P17948 |
|  | Endoglin | ENG | P17813 |
|  | Placental growth factor (PlGF) | PGF | P49763 |
| Moawad et al. (2002) (Ref. 77) | Alkaline phosphatase (ALP) | ALPL | P05186 |
|  | Alpha-fetoprotein (AFP) | AFP | P02771 |
|  | Corticotropin-releasing hormone or factor (CRH, CRF or Corticoliberin) | CRH | P06850 |
| Neggers et al. (2000 ) (Ref. 78) | Alpha-fetoprotein (AFP) | AFP | P02771 |
|  | Zinc levels \* |  |  |
| Ong et al. (2000)  (Ref. 79) | Pregnancy associated plasma protein (PAPP-A or Pappalysin-1) | PAPPA | Q13219 |
|  | Free beta-human chorionic gonadotropin (beta-hCG) fbhCG (Choriogonadotropin subunit beta 3) | CGB3 | P0DN86 |
| Ozer et al. (2005)  (Ref. 80) | Pregnancy associated plasma protein (PAPP-A or Pappalysin-1) | PAPPA | Q13219 |
|  | C-reactive protein | CRP | P02741 |
| Ozgu-Erdinc et al. (2014) (Ref. 81) | Alkaline phosphatase (ALP) | ALPL | P05186 |
|  | Lactate dehydrogenase (LDH) | LDHA | P00338 |
|  | Ferritin | FTL | P02792 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | C-reactive protein | CRP | P02741 |
|  | Ceruloplasmin | CP | P00450 |
| Parry et al. (2020) (Ref. 82) | Fibronectin | FN1 | P02751 |
|  | Extracellular matrix protein 1 | ECM1 | Q16610 |
|  | Laminin subunit alpha-3 | LAMA3 | Q16787 |
|  | Calsyntenin-1 | CLSTN1 | O94985 |
| Parry et al. (2014) (Ref. 83) | Apolipoprotein M (APOM) | APOM | O95445 |
|  | Kininogen-1 (KNG1) | KNG1 | P01042 |
|  | Pregnancy zone protein | PZP | P20742 |
|  | Corticosteroid-binding globulin | SERPINA6 | P08185 |
|  | Prothrombin | F2 | P00734 |
|  | Retinol-binding protein 4 | RBP4 | P02753 |
|  | Hyaluronan-binding protein 2 | HABP2 | Q14520 |
|  | N-acetylmuramoyl-L-alanine amidase | PGLYRP2 | Q96PD5 |
|  | Ficolin-3 | FCN3 | O75636 |
|  | Carboxypeptidase N catalytic chain | CPN1 | P15169 |
|  | Pappalysin-1 | PAPPA | Q13219 |
| Pawelczyk et al. (2010) (Ref. 84) | Toll-like receptor 4 (TLR4) | TLR4 | O00206 |
| Pearce et al. (2010) (Ref. 85) | Corticotropin-releasing hormone (CRH or Corticoliberin) | CRH | P06850 |
|  | Macrophage migration inhibitory factor (MIF) | MIF | P14174 |
|  | Tumour necrosis factor alpha (TNF-a) | TNF | P01375 |
|  | C-reactive protein | CRP | P02741 |
|  | Interleukin 1 beta (IL-1β) | IL1B | P01584 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
| Pihl et al. (2009)  (Ref. 86) | Pregnancy-specific beta-1-glycoprotein (SP1) | PSG1 | P11464 |
| Pitiphat et al. (2005) (Ref. 87) | C-reactive protein | CRP | P02741 |
| Puchner et al. (2011) (Ref. 88) | Interleukin 1 beta (IL-1β) | IL1B | P01584 |
|  | Interleukin 10 (IL-10) | IL10 | P22301 |
|  | Interleukin-18 | IL-18 | Q9NQ49 |
| Puchner et al. (2012) (Ref. 89) | Tumour necrosis factor alpha (TNF-a) | TNF | P01375 |
|  | Cytochrome C | CYCS | P99999 |
| Rahkonen et al. (2010) (Ref. 90) | Insulin-like growth factor-binding protein 1 (IGFBP-1) | IGFBP1 | P08833 |
| Rosen et al. (2001) (Ref. 91) | Thrombin–antithrombin (TAT) \* |  |  |
| Ruiz et al. (2016)  (Ref. 92) | Corticotropin-releasing hormone (CRH or Corticoliberin) | CRH | P06850 |
| Ruiz et al. (2012)  (Ref. 93) | Interleukin-1 receptor antagonist protein | IL1RN | P18510 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Interleukin 10 (IL-10) | IL10 | P22301 |
| Saade et al. (2016) (Ref. 94) | Insulin-like growth factor-binding protein 4 | IGFBP4 | P22692 |
|  | Sex hormone-binding globulin | SHBG | P04278 |
| Shin et al. (2016)  (Ref. 95) | Insulin-like growth factor-binding protein 1 (IGFBP-1) | IGFBP1 | P08833 |
|  | Insulin-like growth factor-binding protein 3 (IGFBP-3) | IGFBP3 | P17936 |
|  | Insulin-like growth factor I (IGF-1) | IGF1 | P05019 |
| Smith et al. (2002) (Ref. 96) | Pregnancy associated plasma protein (PAPP-A or Pappalysin-1) | PAPPA | Q13219 |
|  | Free beta-human chorionic gonadotropin (beta-hCG) fbhCG (Choriogonadotropin subunit beta 3) | CGB3 | P0DN86 |
| Soni et al. (2019)  (Ref. 97) | Free beta-human chorionic gonadotropin (beta-hCG) fbhCG (Choriogonadotropin subunit beta 3) | CGB3 | P0DN86 |
| Sorokin et al. (2010) (Ref. 98) | Matrix metalloproteinase-9 | MMP9 | P14780 |
|  | C-reactive protein | CRP | P02741 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
| Straughen et al. (2012) (Ref. 99) | Vascular endothelial growth factor receptor 1 | FLT1 | P17948 |
| Tamura et al. (1996) (Ref. 100) | Zinc, Copper, iron \* |  |  |
|  | Ferritin | FTL | P02792 |
|  | Transferrin (Serotransferrin) | TF | P02787 |
|  | Albumin | ALB | P02768 |
|  | C-reactive protein | CRP | P02741 |
|  | Alpha-2-macroglobulin | A2M | P01023 |
|  | Ceruloplasmin | CP | P00450 |
|  | Retinol-binding protein 1 | RBP1 | P09455 |
| Thorsen et al. (2001) (Ref. 101) | Interleukin 1 beta (IL-1β) | IL1B | P01584 |
|  | Tumour necrosis factor alpha (TNF-a) | TNF | P01375 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Interleukin 10 (IL-10) | IL10 | P22301 |
| Vogel et al. (2006) (Ref. 102) | Prorelaxin H2 (or relaxin) | RLN2 | P04090 |
| Wallenstein et al. (2016) (Ref. 103) | Vascular endothelial growth factor receptor 1 | FLT1 | P17948 |
|  | Tumour necrosis factor receptor 1 (TNFR1) | TNFR1 | P19438 |
|  | Interleukin-2 receptor subunit alpha | IL2RA | P01589 |
| Whitcomb et al. (2009) (Ref. 104) | Granulocyte colony-stimulating factor (GCSF) or macrophage (GM-CSF) | CSF2 | P04141 |
| Zhang et al. (2017) (Ref. 105) | Complement decay-accelerating factor (CD55) | CD55 | P08174 |
|  | Integrin alpha-M | ITGAM or CD11B | P11215 |
|  | Hyaluronic acid receptor CD44 | CD44 | P16070 |
|  | C-X-C chemokine receptor type 1 | CXCR1 | P25024 |
|  | C-C chemokine receptor type 2 | CCR2 | P41597 |
| Zhu and Yang (2018) (Ref. 106) | C-reactive protein | CRP | P02741 |
|  | Interleukin 6 (IL-6) | IL6 | P05231 |
|  | Macrophage migration inhibitory factor (MIF) | MIF | P14174 |

\*= no UniProt IDs were identified for nonesterified (free) fatty acids (NEFAs), iron, copper, zinc, thrombin-antithrombin (TAT) and advanced glycation end products (AGEs).

Table S4. Preterm birth metabolomics targeted methods reported in maternal biomarker discovery literature (n=7).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Metabolites Identified | Phenotype | Sample type | Total number of maternal participants | Technology/  technique | P value |
| Patil et al. (2021)  (Ref. 107) | 11-deoxycorticosterone (DOC) | PTB (<32 weeks) | Serum | 93  [n= 28 < 32 weeks, n= 40 between 32 - 36 weeks and n=25 > 37 weeks] | UPLC/MS-MS | NA |
| [Eick et al. (2020)](#_ENREF_30)  (Ref. 108) | 8-iso-prostaglandin F2α (8-iso-PGF2α) and prostaglandin F2α (PGF2α) | PTB  (<37 weeks) | Urine | 469  [PTB n=50, control n=396] | stable isotype  dilution gas chromatography-negative ion chemical ionization-mass  spectrometry | P <0.05 |
| [Rosen et al. (2019)](#_ENREF_135)  (Ref. 109) | Free 8-iso-PGF2α (including its metabolite: 2,3-dinor-5,6-  dihydro-15-F2 t-isoprostanes) and PGF2α. | PTB  (<37 weeks) | Urine | 740  [PTB n=61, control n=679] | gas chromatography negative  ion chemical ionization-mass spectrometry | NA |
| [Ferguson et al. (2014)](#_ENREF_39)  (Ref. 110) | Phthalates | PTB  (<37 weeks) | Urine | 482  [PTB n=130, control n=352] | Solid-phase extraction (SPE) and mass spectrometry | NA |
| [Giannella et al. (2011)](#_ENREF_46)  (Ref. 111) | Nitric oxide metabolite (NOx) | PTL  (<34 weeks) | Cervical and gingival swabs | 820  [PTL n=400, control n=420] | Griess reaction | NA |
| [Adibi et al. (2009)](#_ENREF_1)  (Ref. 112) | Mono-2-ethylhexyl phthalate  Mono-2-ethyl-5-oxohexyl phthalate | PTB  (<37 weeks) | Urine | 441 | Solid-phase extraction (SPE) and mass spectrometry | NA |
| [Longini et al. (2007)](#_ENREF_87)  (Ref. 113) | F2-IP (Isoprostanes) | PPROM  (<37 weeks) | Amniotic fluid | 113  [PPROM n=16, no PPROM n=97] | Immunoassay | p<0.0001 |

UPLC/MS-MS = ultraperformance liquid chromatography-tandem mass spectrometry.

Table S5. Top significant pathways (FDR p<0.05, or p<0.05 for genomics) of biomarkers reported in PTB omics literature using Reactome pathway analysis tool (Refs 114, 115).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Omics | Pathway identifier | Pathway name | Entities found | Entities p | Entities FDR |
| Genomics | R-HSA-373080 | Class B/2 (Secretin family receptors) | 2 | 0.003784 | 0.198288 |
| Transcriptomics | R-HSA-9029569 | NR1H3 & NR1H2 regulate gene expression linked to cholesterol transport and efflux | 5 | 2.47E-04 | 0.019023 |
| Proteomics | R-HSA-381426 | Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) | 20 | 1.11E-16 | 7.18E-14 |
| Metabolomics | R-HSA-425407 | SLC-mediated transmembrane transport | 20 | 6.63E-07 | 5.02E-04 |

Chart, histogram

Description automatically generated

**Figure S1**. Distribution of gestation (in weeks) threshold applied for PTB in omics biomarker studies identified in this review. This plot was generated using ‘Matplotlib’ v3.3.3 package in Python 3.8.

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