

Supporting table 1.

Magnetic Cell Sorting (MACS) with different vascular surface markers.

Marker	Number of samples	ml blood per sample	Number of fetal cells identified	Fetal cells/ 10 ml blood
CD105*	7	12	27 fetal cells (0, 1, 1, 4, 5, 6, 10)	3.2
CD34*	7	12	3 fetal cells (0, 0, 0, 0, 0, 1, 2)	0.36
CD141	6	24	8 fetal cells (0, 0, 0, 1, 2, 5)	0.56
CD146	4	24	0 fetal cells (0, 0, 0, 0)	0

*) 7 split samples: 12 ml for CD105 selection, 12 ml for CD34 selection.

Supplementary table 2. Literature search on the 39 genes overexpressed in fetal cells

Gene Name	Full name and Protein function(genecards)	Expression in placenta	Functions related directly to placenta	Functions which also occur in placenta	Function in the endothelium
FIGD	<p>Vascular endothelial growth factor-D</p> <p>C-fos induced growth factor (FIGF)</p> <p>Active in angiogenesis, lymphangiogenesis, and endothelial cell growth</p>	Highly expressed in all types of extravillous trophoblasts.[1]	Promotes vessel formation in connection with placentation.[1]		Growth factor active in angiogenesis, lymphangiogenesis and endothelial cell growth, stimulating their proliferation and migration and also has effects on the permeability of blood vessels.[2]
CRABP1	<p>Cellular retinoic acid binding protein-1</p> <p>specific binding protein for a vitamin A family member and is thought to play an important role in retinoic acid-mediated differentiation and proliferation processes</p>	Expressed in trophoblasts of the porcine placenta.[3]			
PBLD	Phenazine biosynthesis-like protein domain containing				
SMC3	Structural maintenance of chromosomes 3				

HAMP	<p>Hepcidin antimicrobial peptide</p> <p>Involved in the maintenance of iron homeostasis</p>	
CDC42 placental isoform	<p>A small GTPase of the Rho subfamily, which regulates signaling pathways that control diverse cellular functions including cell morphology, migration, endocytosis, and cell cycle progression</p>	<p>Placental isoform of CDC-42.[4] Important for migration of extravillous trophoblasts.[5]</p>
PF4	<p>Its major physiologic role appears to be neutralization of heparin-like molecules on the endothelial surface of blood vessels, thereby inhibiting local antithrombin III activity and promoting coagulation. As a strong chemoattractant for neutrophils and fibroblasts, PF4 probably has a role in inflammation and wound repair</p>	<p>Inhibits endothelial cell proliferation.[6] Neutralization of heparin-like molecules on the endothelial surface of blood vessels.[7]</p>

CD33	Putative adhesion molecule of myelomonocytic-derived cells that mediates sialic-acid-dependent binding to cells			
F11R	An important regulator of tight junction assembly in epithelia. In addition, the encoded protein can act as follows: (1) a receptor for reovirus; (2) a ligand for the integrin LFA1, involved in leukocyte transmigration; and (3) a platelet receptor	Moderately expressed in placenta.[8]		Endothelial cell-to-cell adhesion. Localized at tight junctions of epithelial and endothelial cells. Plays a role in regulating leukocyte transmigration across endothelial cell surfaces.[9,10]
MCAM	Plays a role in cell adhesion and in cohesion of the endothelial monolayer at intercellular junctions in vascular tissue	Expressed strongly in extravillous trophoblasts.[11,12]	Associated with pre-eclampsia.[11]	Plays a role in cell adhesion, and in cohesion of the endothelial monolayer at intercellular junctions in vascular tissue.[13]
JUN	A transcription factor that recognizes and binds to the enhancer heptamer motif 5'-TGA[CG]TCA-3'	Expressed in extravillous trophoblasts.[14]	Regulates proliferation and invasion of extravillous trophoblasts.[14]	
JUNB	Transcription factor involved in regulating gene activity	Expressed in extravillous trophoblasts.[14]	Regulates proliferation and invasion of extravillous	

	following the primary growth factor response. Binds to the DNA sequence 5'-TGA[CG]TCA-3'		trophoblasts.[14] Essential for mammalian placentation.[15]	
DLX5	A member of a homeobox transcription factor gene family similar to the Drosophila distal-less gene. The encoded protein may play a role in bone development and fracture healing	Almost exclusively expressed in placenta.[16]		Promotes cell proliferation by up-regulating MYC promoter activity.[17]
ATF4	Transcriptional activator. Binds the cAMP response element (CRE) (consensus: 5'-GTGACGT[AC][AG]-3'), a sequence present in many viral and cellular promoters	Expressed in placenta (shown in rats).[18]		Regulation of angiogenesis.[19]
CLDN6	This gene encodes a component of tight junction strands, which is a member of the claudin family	Expressed in placenta.[20]		Epithelial and endothelial cell-to-cell adhesion.[21] Endothelial cell-to-cell adhesion.[21]
TCF3	The TCF3 gene encodes two basic helix-loop-helix (bHLH) transcription factors, E12 and E47, through	Invasive and extravillous trophoblasts strongly express TCF molecules.[22]	Plays a role in epithelial-mesenchymal transition in trophoblasts.[22]	

	<p>alternative splicing, which are involved in regulation of immunoglobulin gene expression. Plays a major role in determining tissuespecific cell fate during embryogenesis, like muscle or early Bcell differentiation</p>			
PUM2	<p>Sequence-specific RNA-binding protein that regulates translation and mRNA stability by binding the 3'-UTR of mRNA targets. Its interactions and tissue specificity suggest that it may be required to support proliferation and selfrenewal of stem cells by regulating the translation of key transcripts</p>			
IL7R	<p>Interleukin 7 receptor</p>	<p>Expression in trophoblast cells.[23,24]</p>	<p>Angiogenesis.</p>	<p>Expression in microvascular endothelial cells.[25] Promotes lymphangiogenesis in lung cancer.[26]</p>
SELE	<p>Leukocyte-endothelial cell adhesion</p>	<p>Expression in EVT.[27] Expression at the fetal-maternal interface in the</p>		<p>It is found in cytokine-stimulated endothelial cells and is thought to</p>

	<p>molecule</p> <p>Cell-surface glycoprotein having a role in immunoadhesion. Mediates in the adhesion of blood neutrophils in cytokine-activated endothelium through interaction with PSGL1/SELPLG. May have a role in capillary morphogenesis</p>	<p>murine placenta.[28]</p>		<p>be responsible for the accumulation of blood leukocytes at sites of inflammation by mediating the adhesion of cells to the vascular lining.[29]</p>
ACTB	<p>Beta actin</p> <p>This actin is a major constituent of the contractile apparatus and one of the two nonmuscle cytoskeletal actins.</p>			
TNC	<p>Tenascin C</p> <p>Extracellular matrix protein implicated in guidance of migrating neurons as well as axons during development, synaptic plasticity as well as neuronal regeneration</p>	<p>Expressed in the villous stroma in the placenta.[30,31]</p>	<p>Angiogenesis, involved in transdifferentiation of tumor cells to endothelial cells. Involved in tissue morphogenesis.[32]</p>	<p>Involved in tumor angiogenesis. Plays a vital role in cardiac and arterial injury.[32]</p>

CTNNB1	<p>catenin (cadherin-associated protein), beta 1</p> <p>The protein encoded by this gene is part of a complex of proteins that constitute adherens junctions (AJs). AJs are necessary for the creation and maintenance of epithelial cell layers by regulating cell growth and adhesion between cells.</p>	<p>Wnt/β-catenin/TCF plays a critical role in invasive trophoblast differentiation.[22]</p> <p>Expressed in villous trophoblasts.[33]</p>		<p>Endothelial cell to cell junctions.[34]</p>
HMGA1	<p>High mobility group AT-hook</p>	<p>Expressed in EVT's invading the maternal decidua.[35]</p>	<p>Promotes tumor progression and mesenchymal transition of human epithelial cells.[36]</p>	<p>Hypoxia increases expression of HMG I(Y) in human vascular endothelium (in the cell line HUVEC).[37]</p>
PDGFC	<p>platelet-derived growth factor alpha polypeptide</p>	<p>Other PDGFs and receptors are expressed in the placenta.[38]</p>		<p>Expression in the arterial wall and cultured vascular cells.[39]</p>
NCAM1	<p>Neural cell adhesion molecule 1</p>	<p>Expressed in the intra-arterial(endovascular) trophoblasts[40]</p> <p>Expressed in the placental[41]</p>	<p>Helps maintaining the utero-placental blood flow[40]</p>	<p>CD56 positive natural killer(NK) cells is a part of the immunessystem in the placenta[41]</p> <p>Expressed in tumor derived endothelial cells and progenitor endothelial cells. Important for angiogenese and vessel formation. [42]</p>
CD9	<p>CD9 molecule</p>	<p>CD9 is expressed in extravillous trophoblast</p>	<p>Important for migration of extravillous</p>	<p>CD9 is expressed in the endothelium[46,47]</p>

		[43,44]	trophoblast[45]	CD9 is involved in endothelial cell adhesion and migration during lesion repair and angiogenesis[48]
MMP9	Matrix metalloproteinase	Expressed in placenta [49] Expressed in EVT's [50]	Important for trophoblast invasion[50,51]	Expressed in endothelial cells. Important for angiogenesis [52]
OLIG2	Oligodendrocyte lineage transcription factor 2			
EN1	Engrailed homeobox 1			
CRYL1	Crystallin, lambda 1			
SELPLG	Selectin P ligand	Highly expressed in placenta [53]		Cell adhesion molecule on activated endothelial cells of the inner surface of blood vessels. Facilitates trophoblast adhesion and migration in the uterine vasculature.[54]
CD68	CD68 molecule	Hofbauer cells, macrophages in placenta [55]	Invasion of macrophages(hofbauer) immune cells into the decidua are prominent processes in the first weeks after fertilization.[56]	Might have a function in the decidua vascularization.[56]
COL1A2	Collagen, type I, alpha 2	Expressed in placenta[57]		

SMC3	structural maintenance of chromosomes 3		
KCNQ4	potassium voltage-gated channel, KQT-like subfamily, member 4 . Probably important in the regulation of neuronal excitability	Expressed in placenta[58,59]	Probably plays a function in vasularization of the placenta[58,59]
FOXA2	Forkhead box A2		
CRIP1	Cysteine-rich protein 1		
GATA5	GATA binding protein 5		
SOX13	SRY (sex determining region Y)-box 13	Expressed in the spongiotrophoblast layer of the placenta. [60]	High levels of expression of Sox-13 in the arterial walls during embryonic developoment(mice)[61]

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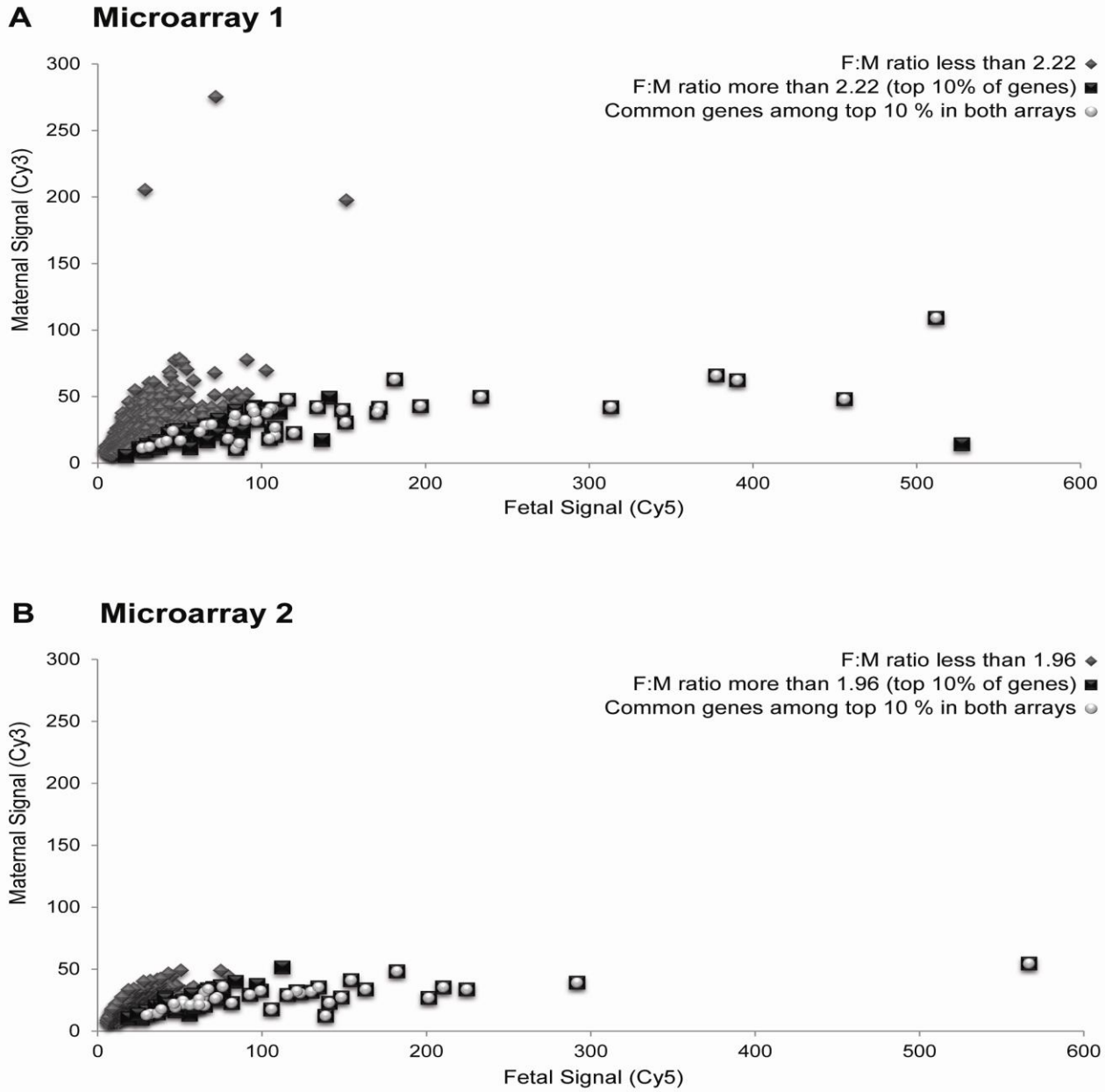
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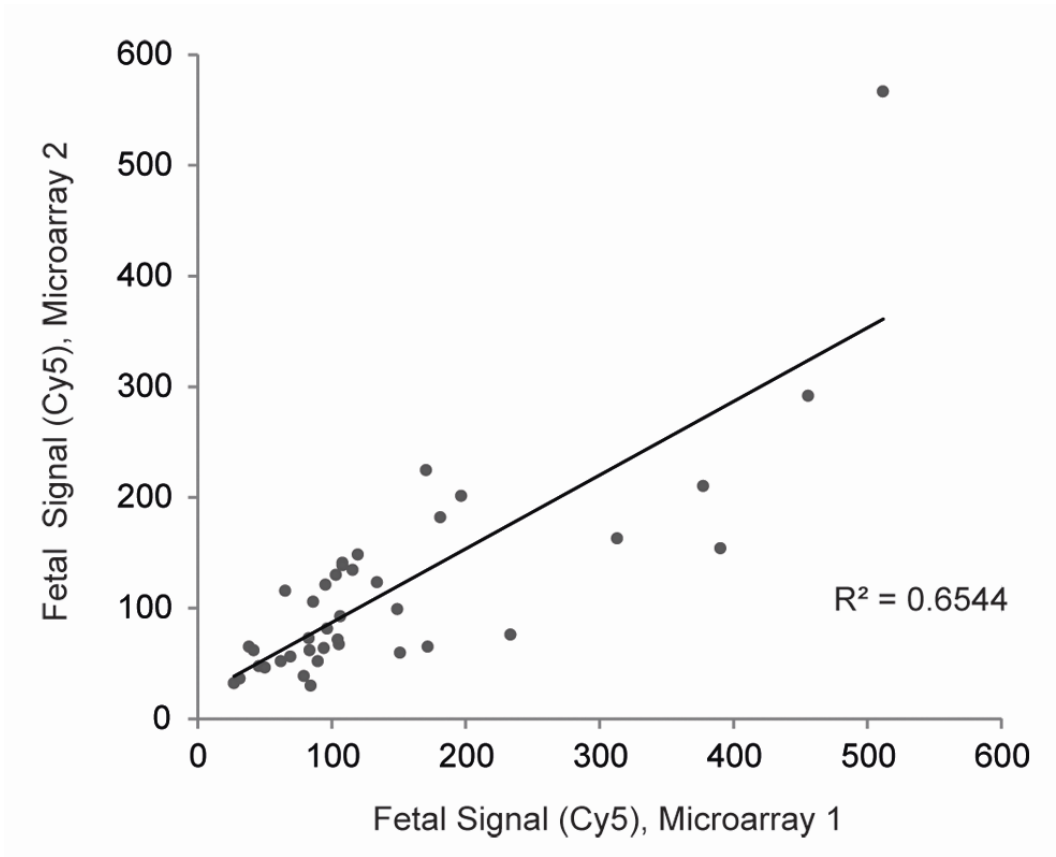
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Supplementary figure 1: Comparison of fetal signals versus maternal signals on the 2 PIQOR microarrays.



The raw fetal signal (Cy5) is plotted against the raw maternal signal (Cy3) for array 1 (fig. 2A) and array 2 (fig. 2B). Genes which had a gene ratio CV > 60% were omitted. 760 genes are plotted in 2A and 784 genes are plotted in 2B. The Squares indicates the 10% genes with the highest fetal/maternal ratio, Rhombus indicates the 90% genes with a lower fetal/maternal ratio (below 2.22 and 1.96, respectively) and the circles indicates genes that are in the top 10% of ratios in both microarrays.

Supplementary figure 2: Comparison of fetal (Cy5) signals for overexpressed genes in microarray 1 and 2.



Fetal signal (Cy5) for the 10% of genes with the highest fetal/maternal ratios in both microarray 1 and 2 are plotted against each other (39genes).