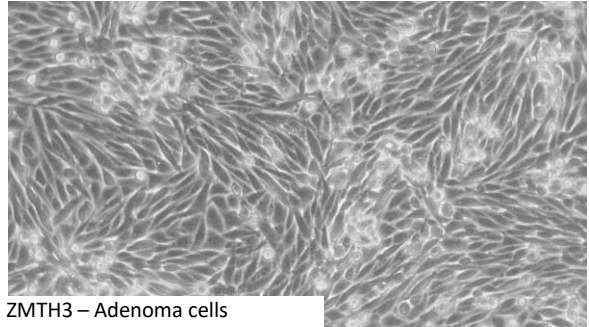
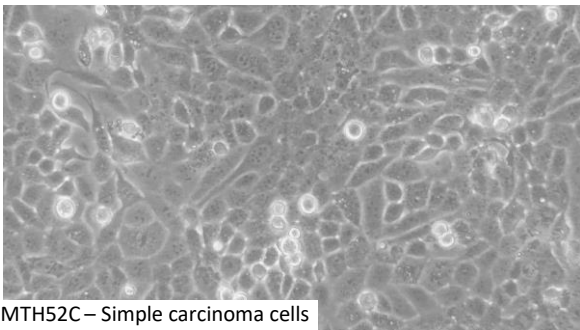


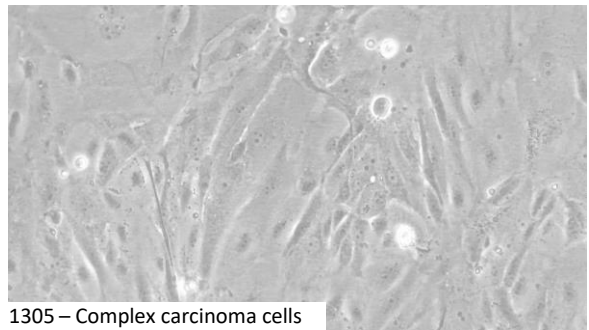
MTH53A - Normal mammary cells



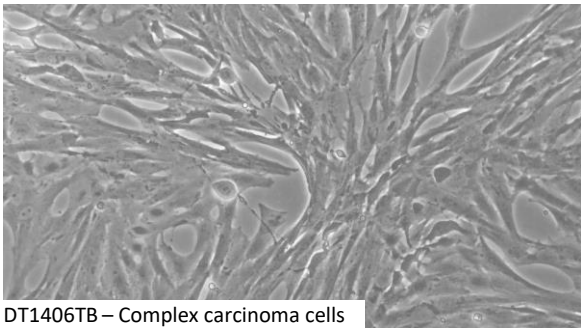
ZMTH3 - Adenoma cells



MTH52C - Simple carcinoma cells



1305 - Complex carcinoma cells



DT1406TB - Complex carcinoma cells

Additional file 1. Morphology of the canine mammary cell lines used in our study. While the cell lines MTH53A and MTH52C have the typical epithelial 'cobblestone'-appearance the complex carcinoma cell lines show an elongated morphology, with the adenoma cell line showing an intermediate growth pattern. Inverted microscopy; 100x magnification.

Additional file 2. Top 10 differentially over- and under-represented proteins identified in carcinoma WCLs vs healthy control

Over-represented proteins											
MTH52C vs MTH53A				1305 vs MTH53A				DT1406TB vs MTH53A			
Accession	Protein	Log2FC	Adj. P-value	Accession	Protein	Log2FC	Adj.P-value	Accession	Protein	Log2FC	Adj. P-value
A0A8I3P1M0	DCTP1	9.513	7.55E-05	A0A8I3MKP5	SERPINB5	11.184	1.06E-06	A0A8I3RXX3	NDUFA4L2	9.627	4.33E-05
A0A8I3P452	CA3	8.004	1.57E-04	A0A8I3P342	ISG15	11.148	8.37E-07	A0A8I3PLN9	ADH4	7.849	7.71E-05
A0A8I3Q6P3	TPM4	7.882	8.06E-05	A0A8I3PI03	TSPAN8	10.741	5.71E-04	A0A8I3NAS7	OCIAD2	7.775	2.88E-03
A0A8I3Q497	TPM4	7.749	4.05E-05	A0A8I3MST9	DHRS2	10.636	3.69E-05	A0A8I3NCP2	ACSF2	7.730	9.20E-04
A0A8I3PIK8	AHSG	7.537	6.37E-05	A0A8I3MI64	SULT2B1	10.562	6.80E-06	A0A8I3N4I3	TPBG	7.631	2.77E-04
A0A8P0NQA3	PTMA	7.315	2.40E-05	A0A8I3RSK1	EPCAM	10.081	1.67E-05	A0A8P0TPH2	NN ^b	7.395	5.68E-06
A0A8I3Q8W7	NN ^a	7.170	1.92E-03	A0A8I3PTT4	MYLK	9.804	4.00E-06	A0A8I3N072	SULT1C4	7.128	1.35E-04
A0A8I3NGU2	LOC476816	6.698	1.09E-03	A0A8I3RRG1	HSPB6	9.503	2.74E-05	A0A8I3NXI7	CASP14	7.041	1.69E-03
A0A8I3PZB0	MDK	6.614	1.05E-04	A0A8I3PLN9	ADH4	9.464	1.40E-05	A0A8I3NW79	PTK2B	6.784	9.42E-04
A0A8P0S8Q7	RTN4	6.397	9.00E-06	J9NV12	BST2	9.453	1.51E-05	A0A8I3PPA0	PTGIS	6.691	2.00E-06

Under-represented proteins											
MTH52C vs MTH53A				1305 vs MTH53A				DT1406TB vs MTH53A			
Accession	Protein	Log2FC	Adj. P-value	Accession N ^a	Protein	Log2FC	Adj.P-value	Accession	Protein	Log2FC	Adj. P-value
A0A8I3PDZ7	RTCB	-6.061	3.80E-05	A0A8I3SAW2	CHAF1B	-8.716	4.72E-06	A0A8I3PVE8	LOC119868340	-6.999	5.00E-04
A0A8I3PYS5	EIF4G1	-5.624	3.89E-04	A0A8I3N128	CDK2	-7.813	1.96E-06	A0A8I3RRM5	SLC7A5	-6.557	7.39E-04
A0A8I3N1X7	PLRG1	-5.528	1.40E-06	A0A8I3NQ76	CYP39A1	-7.234	6.89E-07	A0A8I3S5W2	MID1	-6.256	3.59E-04
A0A8I3NQ76	CYP39A1	-5.342	1.07E-06	A0A8I3MM38	FBL	-7.114	3.34E-05	A0A8I3P3E3	TGM3	-6.058	2.08E-04
A0A8I3RWC5	PLEKHG4	-5.073	4.79E-05	A0A8I3PVE8	LOC119868340	-7.090	4.17E-04	A0A8I3PDZ7	RTCB	-6.013	1.15E-03
A0A8P0STD7	NN ^c	-5.069	6.21E-03	A0A8I3Q3M7	CDC45	-7.065	4.95E-04	A0A8I3NSD1	CUBN	-5.952	4.36E-05
A0A8P0NNH4	TENM3	-4.901	1.33E-04	A0A8I3MU85	TIMM50	-6.760	7.95E-05	A0A8I3NZL8	CLDND1	-5.828	4.65E-03
A0A8I3S0T5	CEBPZ	-4.729	6.27E-05	A0A8P0SH46	CASB	-6.755	1.88E-06	A0A8I3MVP4	ARFGF3	-5.276	4.37E-05
A0A8I3PJ19	SMARCA4	-4.700	1.07E-05	A0A8I3RTJ1	PRIM2	-6.627	1.18E-05	A0A8P0PC40	USP9X	-5.276	1.65E-02
A0A8I3MKV2	LOC487150	-4.693	3.03E-04	A0A8I3S0M7	DPYD	-6.594	1.00E-06	A0A8I3NR12	CDKN2B	-5.176	1.37E-03

a: Prefoldin subunit 4; b: IF rod domain containing protein; c: 40S ribosomal protein S2

Additional file 3. Top over- and under-represented proteins in WCL- derived proteomes and their association with cancer, according to literature research

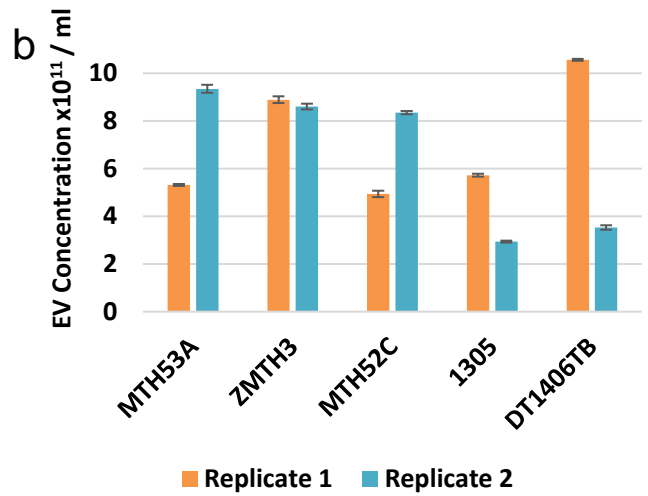
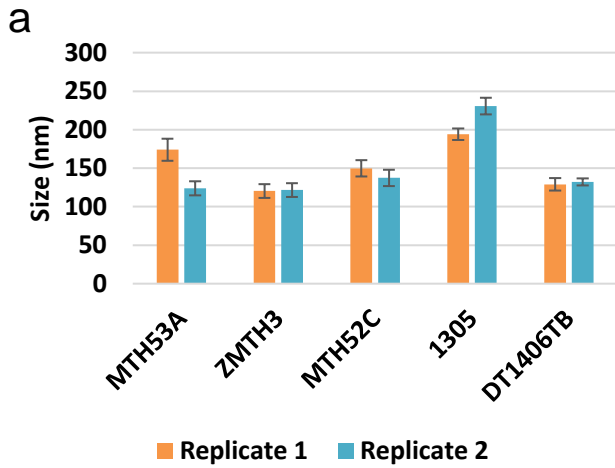
Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
1	ZMTH3	WCL	Over-represented	Eukaryotic translation initiation factor 4C	EIF1AX	A0A8I3QIQ3	Significantly higher in human breast cancer [1], mutations related to malignancy in human thyroid cancer [2, 3].
2	ZMTH3	WCL	Over-represented	Acyl-CoA synthetase family member 2	ACSF2	A0A8I3NCP2	High expression levels in human hepatocellular carcinoma. May estimate prognosis of breast cancer patients [4].
3	ZMTH3	WCL	Over-represented	OCIA domain containing 2	OCIAD2	A0A8I3NAS7	Higher expression in human lung adenocarcinoma. Promotes survival of lung cancer cells [5].
4	ZMTH3	WCL	Over-represented	Tensin 3	TNS3	A0A8I3NH85	Downregulated in human kidney tumours. Correlated negatively with tumour grade, but not tumour size. Metastasis suppressor [6].
5	ZMTH3	WCL	Over-represented	ISG15 ubiquitin like modifier	ISG15	A0A8I3P342	Pro-tumoural and upregulated in melanoma and lung, breast, prostate, nasopharyngeal and oral cancers; tumour suppressor in several cancer types of cervix, blood, and ovaries [7].
6	ZMTH3	WCL	Over-represented	FAM83H protein	FAM83H	H6VX52	Downregulated in cutaneous squamous cell carcinoma (SCC) and correlated with differentiation grade. Overexpression led to decreases in cell migration and invasion [8]. Overexpression increased proliferation and invasion in human osteosarcoma, as well as tumour growth and expression of β -catenin [9]. Overexpressed in liver cancer cells and poor prognostic indicator of human hepatocellular carcinoma [10].
7	ZMTH3	WCL	Over-represented	Peptidyl-prolyl cis-trans isomerase	PPIC	A0A8I3N5K4	Upregulated in human glioma tissue [11].
8	ZMTH3	WCL	Over-represented	Cysteine and glycine rich protein 1	CSRP1	A0A8I3P8T5	Overexpressed in human colon adenocarcinoma in more advanced tumour stages and worst prognosis [12].
9	ZMTH3	WCL	Under-represented	Cytochrome P450 family 39 subfamily A member 1	CYP39A1	A0A8I3NQ76	Downregulation is associated with human hepatocellular carcinoma carcinogenesis, tumour differentiation and poor overall survival [13].
10	ZMTH3	WCL	Under-represented	Calcyphosin	CAPS	P10463	Higher levels of CAPS in human oesophageal squamous cell carcinoma than non-cancerous samples. Positively associated with histological grade and shorter overall survival time [14].
11	ZMTH3	WCL	Under-represented	Dermatopontin	DPT	A0A8I3RS96	Under-expressed in most human colorectal cancer samples [15]. Downregulated in oral squamous cell carcinoma and correlated with cell adhesion and

Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
							invasiveness [16]. Downregulated in human hepatocellular carcinoma [17].
12	ZMTH3	WCL	Under-represented	Dedicator of cytokinesis 4	DOCK4	A0A8I3SCL9	Overexpressed in human stomach adenocarcinoma, with negative impact on prognosis. Associated with tumour immune infiltration [18]. Overexpression in early human breast cancer is associated with aggressive disease and future bone metastasis [19].
13	ZMTH3	WCL	Under-represented	creatine kinase	LOC478277	A0A8I3S958	Poor prognostic factor in overall survival of endometrial cancer patients [20].
14	ZMTH3	WCL	Under-represented	Thioredoxin interacting protein	TXNIP	A0A8I3NKV1	Expressed in tumour from various cancer cells, including breast, colorectal, lung and liver cancer [21].
15	ZMTH3	WCL	Under-represented	Creatine kinase B-type	CKB	P05124	Downregulation is a poor prognosis marker in prostate cancer [22]. Overexpression has a protective effect in colorectal cells [23].
16	MTH52C	WCL	Over-represented	dCTP pyrophosphatase 1	DCTPP1	A0A8I3P1M0	Elevated levels correlate with poor breast cancer prognosis [24, 25].
17	MTH52C	WCL	Over-represented	Carbonic anhydrase	CA3	A0A8I3P452	Overexpression associated with cancer progression in oral squamous cell carcinoma [26].
18	MTH52C	WCL	Over-represented	RAB8A, member RAS onco family	TPM4	A0A8I3Q6P3	Upregulated in lung cancer. Potential marker of ovarian cancer, breast cancer, colon cancer, keratoacanthoma and oesophageal squamous cell carcinoma [27].
19	MTH52C	WCL	Over-represented	RAB8A, member RAS onco family	TPM4	A0A8I3Q497	Described above (nº 18).
20	MTH52C	WCL	Over-represented	Alpha-2-HS-glycoprotein	AHSG	A0A8I3PIK8	High serum levels in gastric cancer patients with favourable diagnostic values; associated with tumour stage [28] Contributes to tumour progression. Its presence in tumour microenvironment may also promote efficient synthesis, secretion and endocytic uptake of exosomes, promoting tumour growth [29].
21	MTH52C	WCL	Over-represented	Prothymosin alpha	PTMA	A0A8PONQA3	Upregulated in oesophageal squamous cell carcinoma tissue [30] and bladder cancer tissue [31].
22	MTH52C	WCL	Over-represented	Prefoldin subunit 4	3 SV	A0A8I3Q8W7	Overexpression is related to better prognosis in colorectal cancer [32].
23	MTH52C	WCL	Over-represented	Folate_rec domain-containing protein	LOC476816	A0A8I3NGU2	Overexpressed in ovarian carcinoma in higher grade than breast cancer effusion samples [33].
24	MTH52C	WCL	Over-represented	Midkine	MDK	A0A8I3PZB0	Overexpression correlated with malignancy in non-small cell lung cancer [34, 35], pancreatic cancer, bladder cancer, melanoma, brain tumours, oesophageal cancer, breast cancer and ovarian cancer [36].

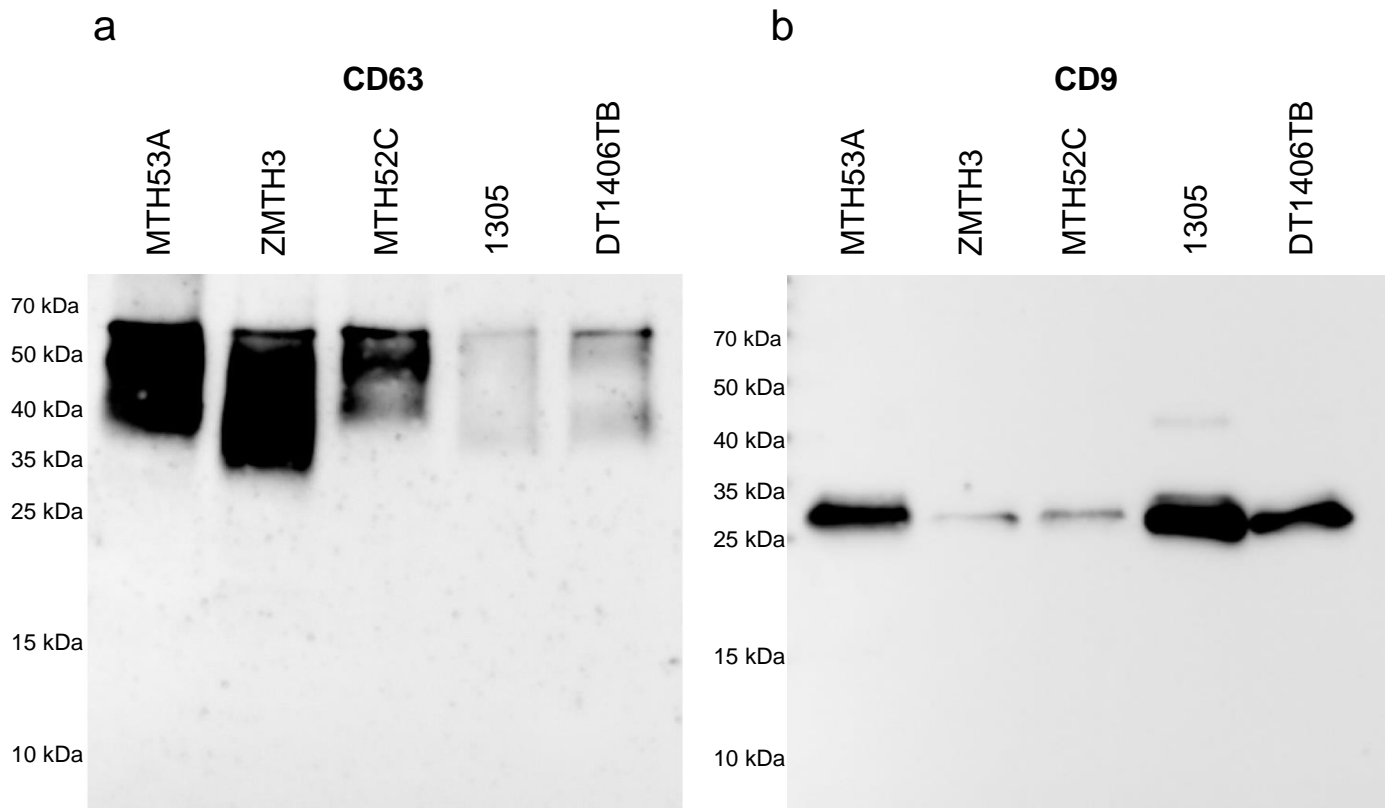
Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
25	MTH52C	WCL	Over-represented	Reticulon	RTN4	A0A8P0S8Q7	Overexpression associated with poor survival in lung, breast, cervical and renal cancer [37].
26	MTH52C	WCL	Under-represented	RNA-splicing ligase RtcB homolog	RTCB	A0A8I3PDZ7	Inhibition improves response to therapy in antioestrogen-resistant breast cancer cells [38].
27	MTH52C	WCL	Under-represented	Eukaryotic translation initiation factor 4 gamma 1	EIF4G1	A0A8I3PYS5	Overexpression in breast cancer is associated with cell survival and DNA damage response, preventing autophagy and apoptosis [39]. Overexpression in lung cancer had immunoregulatory functions [40].
28	MTH52C	WCL	Under-represented	Cytochrome P450 family 39 subfamily A member 1	CYP39A1	A0A8I3NQ76	Described above (nº 9).
29	MTH52C	WCL	Under-represented	Pleckstrin homology and RhoGEF domain containing G4	PLEKHG4	A0A8I3RWC5	Upregulated in human thyroid cancer tissue. Loss of PLEKHG4 enhanced apoptosis ability and stemness properties [41].
30	MTH52C	WCL	Under-represented	40S ribosomal protein S2	3 SV	A0A8P0STD7	Overexpression activate oncogenes involved in tumour development [42].
31	MTH52C	WCL	Under-represented	Teneurin transmembrane protein 3	TENM3	A0A8P0NNH4	Overexpressed in head and neck squamous cell carcinoma, pancreatic adenocarcinoma, thymoma and neuroblastoma. Upregulated in breast and colorectal cancer with metastatic potential. Downregulation associated with poor prognosis in cervical, pancreatic and renal cancer [43].
32	MTH52C	WCL	Under-represented	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4	SMARCA4	A0A8I3PJ19	Overexpression is associated with poor prognosis in many types of tumours, including liver and renal cancer. Silenced or mutated in many cancer cells [44].
33	MTH52C	WCL	Under-represented	Malignant T-cell-amplified sequence	LOC487150	A0A8I3MKV2	Overexpression is associated with malignancy in human breast cancer, lung cancer, oral cancer and mesothelioma [45-47].
34	1305	WCL	Over-represented	Serpin B5	SERPINB5	A0A8I3MKP5	Tumour suppressor activity in breast and prostatic cancers, but tumour progressive features in colorectal cancer [48].
35	1305	WCL	Over-represented	ISG15 ubiquitin like modifier	ISG15	A0A8I3P342	Described above (nº 5).
36	1305	WCL	Over-represented	Tetraspanin	TSPAN8	A0A8I3PI03	Overexpressed and associated with poor prognosis in pancreatic cancer, colon cancer, gastric cancer, liver cancer, lung cancer, breast cancer, ovarian cancer, glioma, melanoma, oesophageal cancer, nasopharyngeal cancer, cancer stem cells [49]. Increases extracellular vesicles release [50].
37	1305	WCL	Over-represented	Dehydrogenase/reductase 2	DHRS2	A0A8I3MST9	Downregulated in oesophageal squamous cell carcinoma and ovarian cancer [51]. Tumour suppressor activity.
38	1305	WCL	Over-represented	Sulfotransferase	SULT2B1	A0A8I3MI64	Overexpressed in colorectal cancer tissue [52] and cervical cancer [53]. Tumour progression activity.

Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
39	1305	WCL	Over-represented	Epithelial cell adhesion molecule	EPCAM	A0A8I3RSK1	Upregulated in solid epithelial cancers and stems cells. Can also be found in disseminated tumour cells and circulating tumour cells [54].
40	1305	WCL	Over-represented	Myosin light chain kinase, smooth muscle	MYLK	A0A8I3PTT4	Upregulated in breast cancer cells, responsible of high proliferative ability with metastatic potential [55].
41	1305	WCL	Over-represented	Heat shock protein family B (small) member 6	HSPB6	A0A8I3RRG1	Overexpressed in lung cancer. Tumour progression protein [56].
42	1305	WCL	Over-represented	Alcohol dehydrogenase 4 (class II), pi polypeptide	ADH4	A0A8I3PLN9	Low expression in hepatocellular carcinoma vs normal tissue. Tumour suppressor protein associated with worse overall survival rate [57].
43	1305	WCL	Over-represented	Bone marrow stromal antigen 2 type 2	BST2	J9NV12	Overexpression associated with bone metastasis formation in human breast cancer [58]. Associated with poor survival in oesophageal, gastric and colorectal cancer [59].
44	1305	WCL	Under-represented	Chromatin assembly factor 1 subunit B	CHAF1B	A0A8I3SAW2	Tumour progression protein in lung cancer [60]. Overexpression associated with poor prognosis in melanoma, prostate cancer, salivary gland tumours, nasopharyngeal cancer, breast cancer, high grade glioma and hepatocellular carcinoma [60].
45	1305	WCL	Under-represented	Cyclin dependent kinase 2	CDK2	A0A8I3N128	Overexpressed with oncogenic activity in ovarian cancer, hepatocellular carcinoma, glioblastoma, prostate cancer, and B cell lymphoma [61].
46	1305	WCL	Under-represented	Cytochrome P450 family 39 subfamily A member 1	CYP39A1	A0A8I3NQ76	Described above (nº 9).
47	1305	WCL	Under-represented	Fibrillarin	FBL	A0A8I3MM38	Overexpression associated with tumour progression in hepatocellular carcinoma [62]. Low expression associated with poor outcome in breast cancer [63].
48	1305	WCL	Under-represented	MAGE domain-containing protein	LOC119868340	A0A8I3PVE8	Oncogenic activity through control of p53 tumour suppressor [64].
49	1305	WCL	Under-represented	Cell division cycle 45	CDC45	A0A8I3Q3M7	Overexpressed in human cancer-derived cells (carcinoma-, sarcoma-, leukaemia-, and lymphoma-derived cells [65], as well as cervical cancer tissue [66].
50	1305	WCL	Under-represented	Mitochondrial import inner membrane translocase subunit TIM50	TIMM50	A0A8I3MU85	Oncogenic protein overexpressed in lung cancer [67] and breast cancer [68].
51	1305	WCL	Under-represented	Carbonic anhydrase	CA5B	A0A8P0SH46	CA5B mRNA upregulation in acute myeloid leukaemia, prostate and renal cell carcinomas [69].
52	1305	WCL	Under-represented	DNA primase large subunit	PRIM2	A0A8I3RTJ1	Overexpressed and associated with poor prognosis in lung cancer [70].
53	1305	WCL	Under-represented	Dihydropyrimidine dehydrogenase [NADP(+)]	DPYD	A0A8I3S0M7	Low expression of DPD mRNA in colorectal tumours, and colorectal liver metastasis [71].
54	DT1406TB	WCL	Over-represented	NDUFA4 mitochondrial complex associated like 2	NDUFA4L2	A0A8I3RXX3	Overexpressed in lung cancer [72], glioblastoma [73] and colorectal cancer [74].
55	DT1406TB	WCL	Over-represented	Alcohol dehydrogenase 4 (class II), pi polypeptide	ADH4	A0A8I3PLN9	Described above (nº 42).

Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
56	DT1406TB	WCL	Over-represented	OCIA domain containing 2	OCIAD2	A0A8I3NAS7	Described above (nº 3).
57	DT1406TB	WCL	Over-represented	Acyl-CoA synthetase family member 2	ACSF2	A0A8I3NCP2	Described above (nº 2).
58	DT1406TB	WCL	Over-represented	Trophoblast glycoprotein	TPBG	A0A8I3N4I3	Overexpressed in lung cancer and gastric cancer, associated with poor prognosis [75].
59	DT1406TB	WCL	Over-represented	Caspase 14	CASP14	A0A8I3NXI7	Overexpressed in breast cancer. Marker of aggressiveness mainly associated with triple negative phenotypes and stemness [76].
60	DT1406TB	WCL	Over-represented	non-specific protein-tyrosine kinase	PTK2B	A0A8I3NW79	Overexpression correlates with reduced survival in pure HER2 breast cancer patients [77].
61	DT1406TB	WCL	Over-represented	Prostacyclin synthase	PTGIS	A0A8I3PPA0	Overexpression associated with poor overall survival in lung, ovarian and gastric cancer. Metastasis predictor [78]. Predictive marker of ovarian cancer [79].
62	DT1406TB	WCL	Under-represented	MAGE domain-containing protein	LOC119868340	A0A8I3PVE8	Described above (nº 48).
63	DT1406TB	WCL	Under-represented	Solute carrier family 7 member 5	SLC7A5	A0A8I3RRM5	Overexpressed in human breast cancer, and correlated with larger tumour size and higher grade [80].
64	DT1406TB	WCL	Under-represented	E3 ubiquitin-protein ligase Midline-1	MID1	A0A8I3S5W2	Low expression in many cancers, including colon and breast cancer, associated with high invasion and metastasis [81].
65	DT1406TB	WCL	Under-represented	Transglutaminase 3	TGM3	A0A8I3P3E3	Upregulated in some tumour tissues like hepatocellular carcinoma, and downregulated in other epithelial carcinomas such as laryngeal carcinoma and oesophageal carcinoma, in which high expression indicates poor prognosis [82]. Candidate tumour suppressor gene in human head and neck cancer [83].
66	DT1406TB	WCL	Under-represented	RNA-splicing ligase RtcB homolog	RTCB	A0A8I3PDZ7	Described above (nº 26).
67	DT1406TB	WCL	Under-represented	Cubilin	CUBN	A0A8I3NSD1	Lower expression is correlated with poor prognosis in renal cell carcinoma. Overexpressed in colorectal cancer [84].
68	DT1406TB	WCL	Under-represented	Claudin domain containing 1	CLDND1	A0A8I3NZL8	Downregulation in breast cancer induces apoptosis caspase-dependent [85].
69	DT1406TB	WCL	Under-represented	ARFGEF family member 3	ARFGEF3	A0A8I3MVP4	Overexpressed in the majority of breast cancers. Knockdown has tumour suppression effect [86].
70	DT1406TB	WCL	Under-represented	ubiquitinyl hydrolase 1	USP9X	A0A8P0PC40	Upregulated in liver cancer cells [87]. Downregulated in cholangiocarcinoma, which contributes to tumorigenesis [88].



Additional file 4. Characterisation of EVs obtained from size exclusion chromatography by nanoparticle tracking analysis (NTA) **a)** Mean particle size (nm) **b)** Concentration of EVs. The graphs show the typical mean particle sizes of extracellular vesicles (EV) with concentrations ranging from 3 to 10 x 10¹¹ particles per ml in the two replicate isolates.



Additional file 5. Western blot for EV markers **a)** CD63 and **b)** CD9 using protein extracts from the isolated EVs. The filter was incubated first with an anti-CD9 and subsequently with an anti-CD63 antibody after mild stripping. The images show the typical smeary pattern for CD63 between 35 and 63kDa and a single ~26kDa band for CD9, with variable expression of the two markers. Images were acquired after 5 minutes of exposure using a Fusion imaging system.

Additional file 6. Top 10 differentially over- and under-represented proteins identified in carcinoma EVs vs healthy control

Over-represented proteins

MTH52C vs MTH53A				1305 vs MTH53A				DT1406TB vs MTH53A			
Accession	Protein	Log2FC	Adj. P-value	Accession	Protein	Log2FC	Adj. P-value	Accession	Protein	Log2FC	Adj. P-value
A0A8I3P684	LUM	11.155	2.26E-03	A0A8I3MHG8	MRPL18	15.114	7.19E-06	A0A8I3P5P0	ECM1	13.144	4.73E-07
A0A8P0TLW8	SSC5D	8.289	3.37E-02	A0A8I3NTB5	CANT1	12.760	3.62E-07	A0A8I3PAS0	HAPLN1	11.965	3.31E-06
A0A8I3NGU2	LOC476816	7.242	3.78E-03	A0A8I3QWY5	LIPH	12.233	1.65E-07	Q28275	FN1	10.712	4.68E-07
	Q6QNF3	7.129	1.77E-02	A0A8I3Q5H9	A2M	12.219	4.89E-07	A0A8I3PUQ0	SBSPON	10.018	1.59E-04
A0A8I3NPK1	FSCN1	6.969	1.37E-03	J9NV12	BST2	11.935	6.70E-05	A0A8I3S4S1	IGFBP6	9.869	1.44E-06
A0A8I3PAS0	HAPLN1	6.534	4.35E-04	A0A8I3RZF7	PSMB10	11.264	6.31E-06	A0A8P0NSQ8	IGFBP6	9.728	3.64E-05
A0A8I3NL35	COL12A1	6.405	2.30E-06	A0A8I3PZB0	MDK	11.262	2.35E-05	A8QWU1	SLPI	9.622	2.12E-05
A0A8I3PBE9	SPON1	6.124	1.76E-04	A0A8I3RVN0	COL14A1	11.132	4.31E-05	A0A8P0TAG1	PACSIN1	9.461	9.47E-06
A0A8P0TJJ1	RELN	6.078	3.90E-02	A0A8P0TLW8	SSC5D	10.690	2.38E-07	A0A8I3Q308	OLFML2B	9.408	4.33E-06
A0A8I3NZ42	CLEC11A	5.667	1.58E-02	A0A8I3S3F7	GPRC5C	10.618	1.75E-05	A0A8I3NGU2	LOC476816	9.315	1.65E-07

Under-represented proteins

MTH52C vs MTH53A				1305 vs MTH53A				DT1406TB vs MTH53A			
Accession	Protein	Log2FC	Adj. P-value	Accession	Protein	Log2FC	Adj. P-value	Accession	Protein	Log2FC	Adj. P-value
A0A8P0SL9	XPO6	-5.010	2.94E-04	Q9XSJ7	COL1A1	-8.277	7.62E-05	A0A8I3PHH6	QPCT	-8.963	4.74E-05
A0A8I3PRZ8	NRCAM	-4.151	4.25E-02	A0A8I3PI61	SLX9	-8.153	4.61E-05	A0A8I3RZY0	LETM1	-7.998	1.42E-04
A0A8I3NRJ5	ELAVL2	-4.016	2.12E-02	A0A8I3QI05	SORD	-8.099	3.46E-04	A0A8P0SUA9	TNN	-7.259	5.05E-05
A0A8I3PMJ4	DIS3L2	-3.638	5.07E-03	A0A8I3P795	SNU13	-7.794	1.15E-03	A0A8I3PX13	H3C4	-7.153	4.04E-05
A0A8I3PCK9	FAT1	-3.429	1.78E-02	A0A8P0SL9	XPO6	-7.770	2.03E-04	A0A8P0SB44	SARS2	-7.035	4.28E-04
A0A8I3S8V0	CCN1	-3.353	1.53E-02	A0A8I3PTI4	TRMT5	-7.309	1.09E-05	Q9XSJ7	COL1A1	-6.740	4.46E-03
A0A8P0NLM5	ACADM	-3.349	3.71E-02	A0A8P0S7F1	HMGA1	-7.216	1.76E-03	A0A8P0SL9	XPO6	-6.686	4.33E-06
	D2YYC0	-3.338	1.78E-02	A0A8P0PAW3	CRTAC1	-6.648	1.81E-04	A0A8P0SQL8	3 SV ^a	-6.671	1.34E-03
A0A8I3RUE8	HGH1	-3.327	3.95E-02	A0A8P0SLA8	COL1A1	-6.606	2.87E-04	E2R6K5	H3-3A	-6.592	1.48E-03
A0A8I3NJ93	AARS2	-3.229	2.07E-02	A0A8I3MER3	4 SV ^a	-6.426	2.29E-04	A0A8P0SET5	WDR3	-6.228	1.94E-05

a: Rad60-SLD domain-containing protein, b: Ribosomal protein L37a.

Additional file 7. Top over- and under-represented proteins in EV- derived proteomes and their association with cancer, according to literature research

Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
71	ZMTH3	EV	Over-represented	CTP synthase	CTPS2	A0A8I3QAX6	Overexpressed in chronic lymphocytic leukaemia, associated with poor prognosis [89].
72	ZMTH3	EV	Over-represented	Galectin-3-binding protein	CANT1	A0A8I3NTB5	Overexpressed in lung cancer, renal cell carcinoma [90, 91] and prostate cancer [92].
73	ZMTH3	EV	Over-represented	Transcobalamin 2	TCN2	A0A8I3PAV5	Low expression has an effect similar to hypoxia. High expression can reverse it [93]. Overexpressed in canine and feline tumour tissues [94].
74	ZMTH3	EV	Over-represented	ISG15 ubiquitin like modifier	ISG15	A0A8I3P342	Described above (nº 5).
75	ZMTH3	EV	Over-represented	Microfibril associated protein 2	MFAP2	A0A8I3MLA0	Overexpressed in bladder cancer, brain and central nervous system cancer, breast cancer, colorectal cancer, oesophageal cancer, gastric cancer, head and neck cancer, lymphoma, melanoma, myeloma, ovarian cancer, pancreatic cancer, sarcoma [95] and hepatocellular carcinoma [96]. Associated with poor prognosis.
76	ZMTH3	EV	Over-represented	ArfGAP with dual PH domains 1	ADAP1	A0A8P0TVC6	Promotes invasive squamous cell carcinoma progression [97] and metastatic colorectal cancer [98].
77	ZMTH3	EV	Over-represented	Zona pellucida like domain containing 1	ZPLD1	A0A8I3PFH2	Associated with pancreatic cancer and breast cancer metastasis [99].
78	ZMTH3	EV	Over-represented	Bone marrow stromal antigen 2 type 2	BST2	J9NVI2	Described above (nº 43).
79	ZMTH3	EV	Over-represented	Interferon induced protein 44	IFI44	A0A8I3MKR1	Correlated with immune infiltration in head and neck squamous cell carcinoma [100].
80	ZMTH3	EV	Over-represented	Serine protease 23	PRSS23	A0A8P0N757	Upregulated in breast cancer cells, prostate cancer, papillary thyroid cancer, pancreatic cancer [101] and gastric cancer [102].
81	ZMTH3	EV	Under-represented	Matrix remodeling-associated protein 8	MXRA8	A0A8I3PNQ7	Cancer-associated marker in pancreatic cancer [103]. Expression correlated with malignancy, metastasis, recurrence and immunosuppressive microenvironment [104].
82	ZMTH3	EV	Under-represented	Angiopoietin like 2	ANGPTL2	A0A8I3N7R9	Tumourigenic role in thyroid cancer cells [105]. Overexpressed in lung cancer, colorectal cancer, prostate cancer and gastric cancer [106]. Dual function (tumour progression/anti tumour immunity) [107].
83	ZMTH3	EV	Under-represented	RAB8A, member RAS onco family	TPM4	A0A8I3Q6P3	Described above (nº 18).
84	ZMTH3	EV	Under-represented	Tenascin N	TNN	A0A8I3NDQ9	Overexpressed in high grade tumours [108]. Novel marker for tumour stroma in low-grade human

Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
85	ZMTH3	EV	Under-represented	RAB8A, member RAS onco family	TPM4	A0A8I3Q497	breast cancer [109]. Elevated in serum of colon and breast cancer [110]. Described above (nº 18).
86	ZMTH3	EV	Under-represented	LamGL domain-containing protein	PTX3	A0A8I3PGJ4	Dual role. Low expression increases susceptibility to mesenchymal and epithelial carcinogenesis. Expression has anti-tumour activity in oesophageal squamous cell carcinoma and colorectal cancer. Pro-tumorigenic role in head and neck tumours, cervical cancer, glioma and hepatocellular carcinoma. Oncogenic protein in breast cancer [111].
87	ZMTH3	EV	Under-represented	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 8, mitochondrial	NDUFB8	A0A8I3NUH5	Low expression in tumour tissues in breast cancer [112].
88	ZMTH3	EV	Under-represented	Plasma retinol-binding protein	RBP4	A0A8P0T552	Downregulation indicates poor prognosis in hepatocellular carcinoma [113]. Associated with advanced tumour stages and grades. Overexpressed in glioblastoma with tumorigenic activity [114].
89	MTH52C	EV	Over-represented	Lumican	LUM	A0A8I3P684	Oncogene in gastric cancer progression. Correlated with poor overall survival. More frequently detected in carcinoma than adenoma cells [115].
90	MTH52C	EV	Over-represented	Folate_rec domain-containing protein	LOC476816	A0A8I3NGU2	Described above (nº 23).
91	MTH52C	EV	Over-represented	Platelet-derived growth factor receptor beta	PDGFRB	Q6QNF3	Overexpressed in metastatic medulloblastoma [116]. High expression in glioblastoma [117].
92	MTH52C	EV	Over-represented	Fascin	FSCN1	A0A8I3NPK1	Overexpressed in multiple cancers such as laryngeal squamous cell carcinoma, lung cancer, oral squamous cell carcinoma, oesophageal squamous cell carcinoma, gastric cancer, hepatocellular carcinoma, colorectal cancer, renal cell carcinoma, urothelial carcinoma, breast cancer and uterine carcinosarcoma [118].
93	MTH52C	EV	Over-represented	Hyaluronan and proteoglycan link protein 1	HAPLN1	A0A8I3PAS0	Overexpressed in pancreatic ductal adenocarcinoma and promotes metastasis [119]. Overexpressed in breast cancer [120], hepatocellular carcinoma [121] and mesothelioma [122]. In gastric cancer, cancer-associated fibroblasts promote tumour invasion through extracellular matrix remodelling [123]. In canine mammary tumours, a significant association between HAPLN1 with early stage canine malignant mammary tumour was reported [124].
94	MTH52C	EV	Over-represented	Collagen type XII alpha 1 chain	COL12A1	A0A8I3NL35	Upregulated in gastric cancer. Elevated expression correlated with invasiveness, metastasis and advanced clinical stage [125]. Upregulated in breast cancer tissues [126].

Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
95	MTH52C	EV	Over-represented	Spondin-1	SPON1	A0A8I3PBE9	Overexpressed in ovarian cancer [127] and pancreatic cancer [128].
96	MTH52C	EV	Over-represented	Reelin	RELN	A0A8P0TJJ1	Silenced in glioblastoma as compared to non-neoplastic tissue [129]. Loss of reelin is associated to poor outcome [130]. Expressed in prostate cancer but not in benign prostate tissue [131].
97	MTH52C	EV	Over-represented	C-type lectin domain containing 11A	CLEC11A	A0A8I3NZ42	High expression predicts favourable prognosis in acute myeloid leukaemia [132]. Associated with development of leukaemia, multiple myeloma, and gastrointestinal tumours [133].
98	MTH52C	EV	Under-represented	Exportin 6	XPO6	A0A8P0SLI9	Upregulation acts as a tumour suppressor in breast cancer [134]. Highly expressed in prostate cancer tissues, with pro-tumour activity [135].
99	MTH52C	EV	Under-represented	Neuronal cell adhesion molecule	NRCAM	A0A8I3PRZ8	Overexpressed in papillary thyroid carcinomas, both in mRNA and protein levels [136]. Overexpressed in high-grade astrocytoma, glioma and glioblastoma tumour tissues; colon cancer, advanced stages of melanoma Low levels observed in neuroblastoma, meningioma, pancreatic adenocarcinoma [137]. Lower expression in gastric cancer tissues in contrast with normal tissues. High NRCAM expression indicates poor prognosis and promotes tumour progression [138].
100	MTH52C	EV	Under-represented	ELAV-like protein	ELAVL2	A0A8I3NRJ5	Tumour suppressor activity. Low expression is associated with cancer progression and chemoresistance in glioblastoma [139].
101	MTH52C	EV	Under-represented	DIS3-like exonuclease 2	DIS3L2	A0A8I3PMJ4	Loss of DIS3L2 is related with tumour progression in both <i>Drosophila</i> and human cells [140].
102	MTH52C	EV	Under-represented	FAT atypical cadherin 1	FAT1	A0A8I3PCK9	Upregulated in acute leukaemia, hepatocellular carcinoma, glioblastoma, and gastric cancer. Downregulated in head and neck squamous cell carcinoma, oesophageal squamous cell carcinoma, breast cancer and cervical cancer [141]. Loss of FAT1 and β -catenin are associated with breast cancer progression, aggressive behaviour and poor prognosis [142].
103	MTH52C	EV	Under-represented	Cellular communication network factor 1	CCN1	A0A8I3S8V0	Upregulated in prostate, ovarian, endometrial, and pancreatic cancer cells [143]. CCN1 expression promote metastasis and tumour progression in triple negative breast cancer, whereas low expression has tumour suppressor activity [144].
104	MTH52C	EV	Under-represented	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	ACADM	A0A8P0NLM5	Low expression in hepatocellular carcinoma, correlating with aggressive clinicopathologic

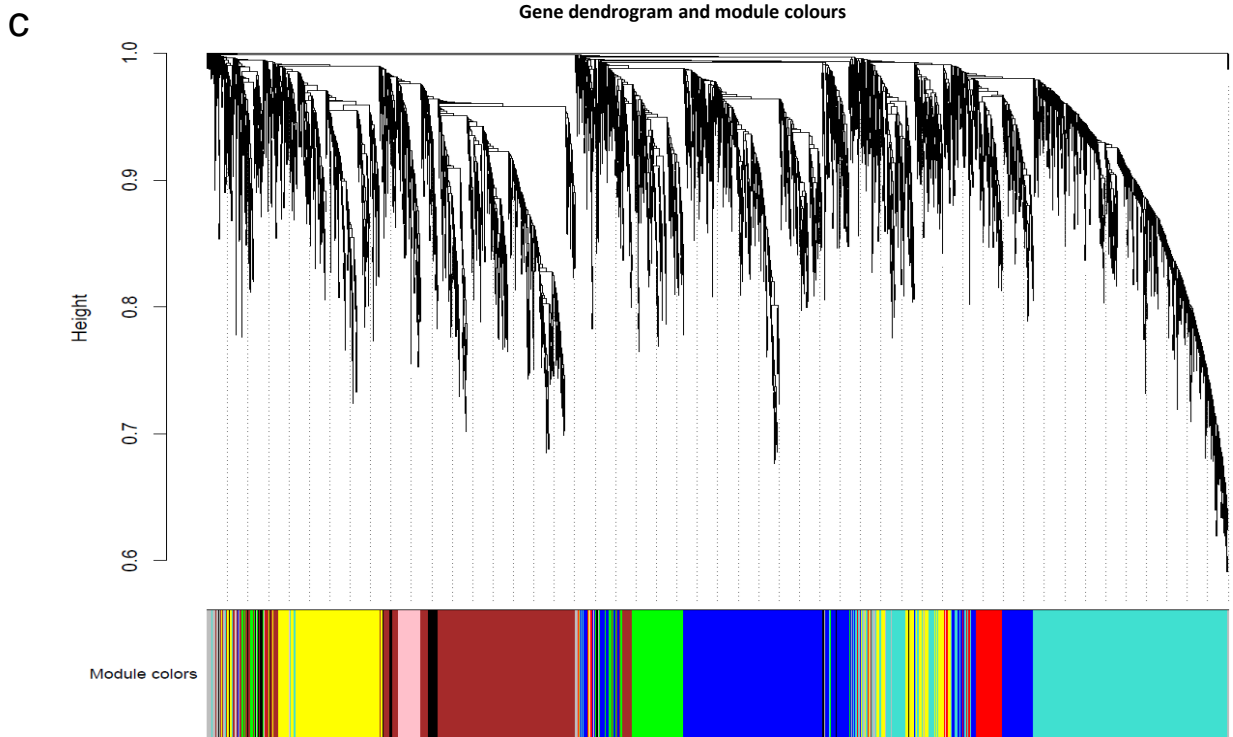
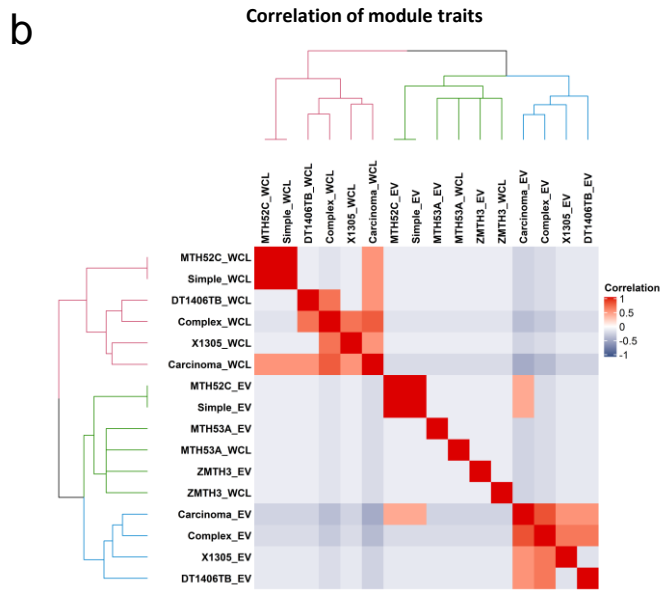
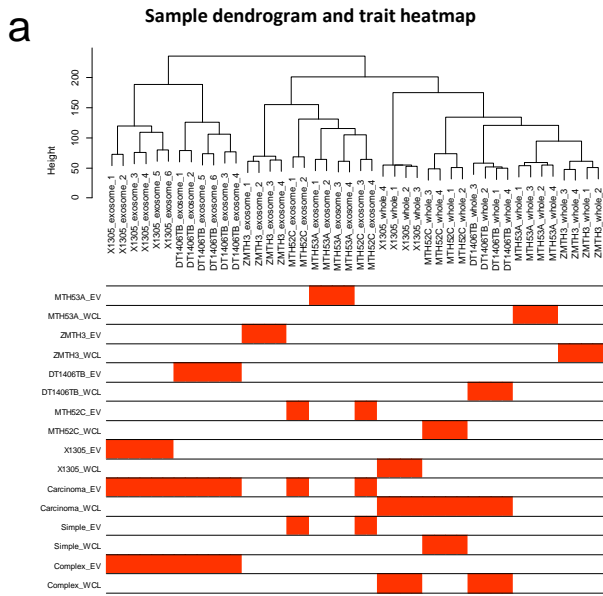
Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
105	MTH52C	EV	Under-represented	Mothers against decapentaplegic homolog	Madh3	D2YYC0	features in patients [145]. Overexpressed in breast cancer tissues, acting as an oncogene [146]. MADH3 expression may have a critical role in tumour suppression in early stages of gastric carcinogenesis. Loss of expression increases susceptibility to tumorigenicity in human gastric cancer [147].
106	MTH52C	EV	Under-represented	Protein HGH1 homolog	HGH1	A0A8I3RUE8	Upregulated in colon adenocarcinoma and rectum adenocarcinoma [148].
107	MTH52C	EV	Under-represented	Alanine--tRNA ligase	AARS2	A0A8I3NJ93	Loss of AARS decreases tumour progression of colon cancer cells [149].
108	1305	EV	Over-represented	Mitochondrial ribosomal protein L18	MRPL18	A0A8I3MHG8	Dysregulated expression of MRPL18 has been correlated with tumour progression in lung cancer [150].
109	1305	EV	Over-represented	Galectin-3-binding protein	CANT1	A0A8I3NTB5	Described above (nº 72). Upregulated mRNA and protein expression in breast cancer tumours, and might be related to worse prognosis [151]. In pancreatic cancer, LIPH is considered a novel unfavourable prognostic marker [152].
110	1305	EV	Over-represented	Lipase H	LIPH	A0A8I3QWY5	Described above (nº 72). Upregulated mRNA and protein expression in breast cancer tumours, and might be related to worse prognosis [151]. In pancreatic cancer, LIPH is considered a novel unfavourable prognostic marker [152].
111	1305	EV	Over-represented	Alpha-2-macroglobulin	A2M	A0A8I3Q5H9	Expression inhibits growth of tumours in mice [153]. Low expression in intrahepatic cholangiocarcinoma was an adverse prognostic factor [154].
112	1305	EV	Over-represented	Bone marrow stromal antigen 2 type 2	BST2	J9NVI2	Described above (nº 43).
113	1305	EV	Over-represented	Proteasome subunit beta	PSMB10	A0A8I3RZF7	Upregulated in breast cancer, affecting the efficacy of neoadjuvant chemotherapy [155].
114	1305	EV	Over-represented	Midkine	MDK	A0A8I3PZB0	Described above (nº 24).
115	1305	EV	Over-represented	Collagen type XIV alpha 1 chain	COL14A1	A0A8I3RVN0	Downregulation associated with aggressive breast cancer subtypes [156]. Overexpressed in liver cancer stem cells [157], and gastric cancer with peritoneal metastasis [158].
116	1305	EV	Over-represented	G protein-coupled receptor class C group 5 member C	GPRC5C	A0A8I3S3F7	Detected in extracellular vesicles from serum of pancreatic ductal adenocarcinoma; candidate biomarker for early pancreatic cancer [159].
117	1305	EV	Under-represented	Collagen alpha-1(I) chain	COL1A1	Q9XSJ7	Increased levels are associated with poor survival and metastasis status in breast cancer [160], colorectal cancer [161], and lung cancer [162]. Knockdown of COL1A1 inhibits metastasis.
118	1305	EV	Under-represented	Sorbitol dehydrogenase	SORD	A0A8I3QJ05	Upregulated in colorectal adenomas and cancer cell lines [163]. In liver cancer, SORD high expression is associated with favourable effects, playing a functional role in hepatocellular suppression [164].

Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
119	1305	EV	Under-represented	Ribonucleoprotein	SNU13	A0A8I3P795	Upregulated in breast cancer tumour samples and negatively correlated with prognosis [165].
120	1305	EV	Under-represented	Exportin 6	XPO6	A0A8P0SLL9	Described above (nº 98).
121	1305	EV	Under-represented	tRNA (guanine(37)-N1)-methyltransferase	TRMT5	A0A8I3PTI4	Upregulated in hepatocellular carcinoma and correlated with poor prognosis [166].
122	1305	EV	Under-represented	High mobility group protein HMG-I/HMG-Y	HMGA1	A0A8P0S7F1	Participates in tumourigenesis and tumour progression. Upregulated in many different tumours including epithelial and mesenchymal tissue-originated tumours. Overexpression is correlated with poor clinical outcome, distant metastasis and advanced tumour stage [167].
123	1305	EV	Under-represented	Cartilage acidic protein 1	CRTAC1	A0A8P0PAW3	Overexpression inhibits tumour progression in bladder cancer, while low expression correlates with poor survival [168].
124	1305	EV	Under-represented	Collagen alpha-1(I) chain	COL1A1	A0A8P0SLA8	Described above (nº 117).
125	DT1406TB	EV	Over-represented	Extracellular matrix protein 1	ECM1	A0A8I3P5P0	Overexpressed in colorectal cancer, bladder cancer, glioblastoma, thyroid cancer, cholangiocarcinoma, and other epithelial malignancies, and it is related to poor prognosis in pancreatic cancer, breast cancer, gastric cancer and hepatocellular cancer [169, 170]. Associated with tumour progression and cancer stem cell maintenance [171].
126	DT1406TB	EV	Over-represented	Hyaluronan and proteoglycan link protein 1	HAPLN1	A0A8I3PAS0	Described above (nº 93).
127	DT1406TB	EV	Over-represented	Fibronectin (Fragment)	FN1	Q28275	Overexpression is correlated with tumour-infiltrating immune cells and therefore poor prognosis in breast cancer [172], gastric cancer [173], head and neck squamous cell carcinoma [174].
128	DT1406TB	EV	Over-represented	Thyroglobulin type-1 domain-containing protein	IGFBP6	A0A8I3S4S1	In most studies, its expression is lower in malignant cells than in normal cells. Inhibitor of tumourigenic and metastatic processes. However, it has been described higher expression in adrenocortical tumours, breast cancer and ovarian cancer [175]. Malignant breast tumours with reduced expression of IGFBP6 and ELOVL5 genes can metastasize with a higher probability due to a more efficient invasion of tumours cells [176].
129	DT1406TB	EV	Over-represented	Insulin like growth factor binding protein 6	IGFBP6	A0A8P0NSQ8	Described above (nº 128).
130	DT1406TB	EV	Over-represented	Protease inhibitor	SLPI	A8QWU1	Highly expressed in gastric cancer tissues, and significantly correlated with survival time, clinical classification and size of the tumour. Involved in metastasis progression [177]. Pro-malignant activity.

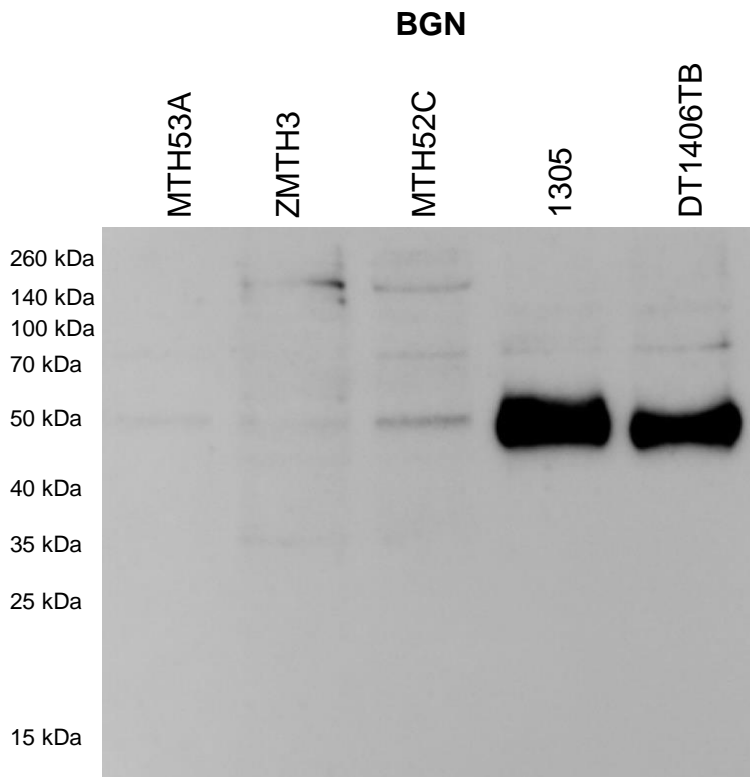
Nº	Cell line	Sample type	Condition	Protein name	Protein abbreviation	Accession number	Association with cancer
131	DT1406TB	EV	Over-represented	Protein kinase C and casein kinase substrate in neurons 1	PACSIN1	A0A8P0TAG1	Overexpression associated with progression of tumours of different histological origin [178]. Described as prognostic tool to predict progression of specific breast cancer subtypes [179, 180]. Negatively correlated with malignant degree of gliomas and positively associated with overall survival [181].
132	DT1406TB	EV	Over-represented	Olfactomedin like 2B	OLFML2B	A0A8I3Q308	Highly upregulated in gastric cancer [182] and hepatocellular carcinoma. May be a prognostic marker in immunotherapy for diverse tumours [183]. Overexpressed in bladder cancer [184].
133	DT1406TB	EV	Over-represented	Folate_rec domain-containing protein	LOC476816	A0A8I3NGU2	Described above (nº 23). Diagnostic marker for papillary thyroid carcinoma [185]. High level is correlated with decreased rate of overall survival in adrenocortical carcinoma, mesothelioma, and brain lower grade glioma, whereas in other types of cancer the overexpression indicates a higher survival rate, including cholangiocarcinoma and colon adenocarcinoma [186]. Expressed in local advanced breast tumours and positively correlated with poor-disease free survival [187].
134	DT1406TB	EV	Under-represented	glutaminy-peptide cyclotransferase	QPCT	A0A8I3PHH6	Overexpressed and associated with poor prognosis in colorectal [188], liver [189], breast, oesophagus, lung, ovary, stomach and uterine cancer. In thyroid, prostate, ovarian and gastric cancer, overexpression is correlated with increased cell survival [190].
135	DT1406TB	EV	Under-represented	Mitochondrial proton/calcium exchanger protein	LETM1	A0A8I3RZY0	Described above (nº 84).
136	DT1406TB	EV	Under-represented	Tenascin N	TNN	A0A8P0SUA9	Described above (nº 117).
137	DT1406TB	EV	Under-represented	Collagen alpha-1(I) chain	COL1A1	Q9XSJ7	Described above (nº 98).
138	DT1406TB	EV	Under-represented	Exportin 6	XPO6	A0A8P0SLL9	Significantly downregulated in nasopharyngeal carcinoma tissues [191].
139	DT1406TB	EV	Under-represented	Ribosomal protein L37a	3 SV	A0A8P0SQL8	Overexpressed in lung cancer, associated with cancer progression [192].
140	DT1406TB	EV	Under-represented	Histone H3	H3-3A	E2R6K5	Overexpression is correlated with poor survival in pancreatic cancer [193], prostate cancer [194]. WDR3 may modulate genome stability in thyroid cancer [195].
141	DT1406TB	EV	Under-represented	WD repeat domain 3	WDR3	A0A8P0SET5	

Additional file 8. Top 20 differentially over- and under-represented proteins identified in complex carcinoma EVs vs healthy control

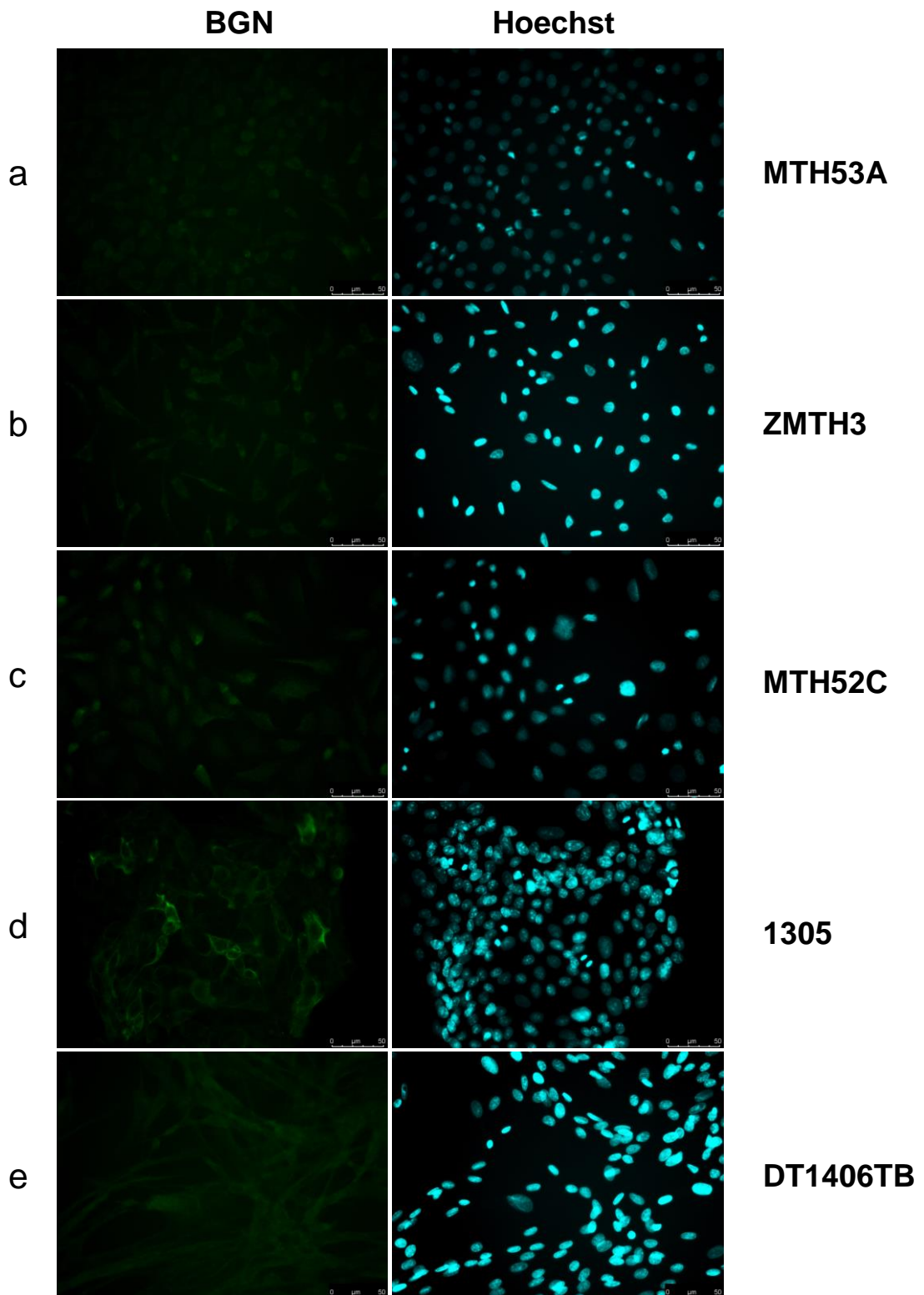
Common over-represented proteins				
Accession number	Protein name	Protein abbreviation	1305 Log2FC	DT1406TB Log2FC
A0A8I3P5P0	Extracellular matrix protein 1	ECM1	10.604	13.144
A0A8P0TAG1	Protein kinase C and casein kinase substrate in neurons 1	PACSIN1	8.357	9.461
A0A8I3MVW9	Actinin alpha 1	ACTN1	8.729	8.593
A0A8I3PFD7	Vascular endothelial growth factor C	VEGFC	8.595	8.504
A8QWU1	Protease inhibitor	SLPI	7.094	9.622
A0A8I3P2C5	Transforming growth factor-beta-induced protein ig-h3	TGFBI	7.130	9.242
A0A8I3PI03	Tetraspanin	TSPAN8	9.109	6.952
A0A8I3R277	Lipoprotein lipase	LIPG	7.959	8.062
A0A8P0P533	Phospholipid scramblase	PLSCR1	9.196	6.351
A0A8I3N0D6	Kinesin light chain	KLC3	8.815	6.479
A0A8I3N4I3	Trophoblast glycoprotein	TPBG	8.303	6.970
A0A8I3NSN5	Fibulin-1	FBLN1	6.716	8.238
A0A8P0S8N5	AE binding protein 1	AEBP1	5.782	9.163
A0A8I3NQQ5	Complement C2	C2	6.548	8.343
A0A8I3P7V9	EGF like repeats and discoidin domains 3	EDIL3	6.214	8.627
A0A8P0TN04	PDZ domain-containing protein	AHNAK	7.860	6.865
A0A8I3MK79	Vasorin	VASN	6.968	7.693
A0A8I3Q3F0	non-specific serine/threonine protein kinase	SLK	6.492	8.125
A0A8I3P614	Stanniocalcin 1	STC1	7.889	6.637
A0A8P0N5R9	Glycoprotein nmb	GPNMB	6.140	8.249
Common under-represented proteins				
Accession number	Protein name	Protein abbreviation	1305 Log2FC	DT1406TB Log2FC
A0A8I3PX13	Histone H3	H3C4	-5.206	-7.153
A0A8P0SET5	WD repeat domain 3	WDR3	-4.857	-6.228
E2R6K5	Histone H3	H3-3A	-4.080	-6.592
A0A8I3S4C9	Interleukin enhancer binding factor 3	ILF3	-5.114	-4.823
A0A8I3PMM3	Cellular tumor antigen p53	TP53	-3.954	-5.924
A0A8P0P879	CSD domain-containing protein	LOC479011	-4.681	-5.156
A0A8I3P7A1	Nucleophosmin/nucleoplasmin 3	NPM3	-5.305	-4.130
A0A8I3P9E1	Tubulin alpha chain	TUBA1C	-3.287	-5.946
A0A8I3P801	Mitogen-activated protein kinase	MAPK7	-4.579	-4.622
A0A8I3NP87	40S ribosomal protein S15	RPS15	-4.872	-4.188
A0A8I3Q7A7	RTF1 homolog, Paf1/RNA polymerase II complex component	RTF1	-5.619	-3.401
A0A8I3Q153	40S ribosomal protein S13	RPS13	-3.164	-5.723
A0A8I3RQK5	Protein phosphatase 2 scaffold subunit Abeta	PPP2R1B	-3.430	-5.398
A0A8I3Q3G4	Jumonji domain containing 7	JMJD7	-5.165	-3.635
A0A8I3MXB4	Ribosome biogenesis protein BRX1 homolog	BRX1	-4.577	-4.196
A0A8P0SB07	RRM domain-containing protein	LOC475399	-3.845	-4.729
A0A8I3QL49	Tubulin alpha chain	LOC610636	-4.273	-4.239
A0A8I3N3V4	Cyclin dependent kinase 1	CDK1	-4.702	-3.694
A0A8I3MVT8	BSD domain containing 1	BSDC1	-4.397	-3.932
A0A8I3RVI6	Exportin 5	XPO5	-4.058	-4.264



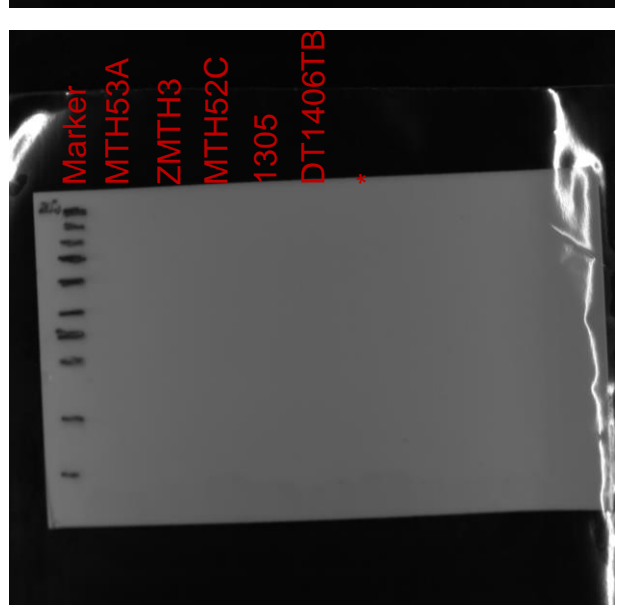
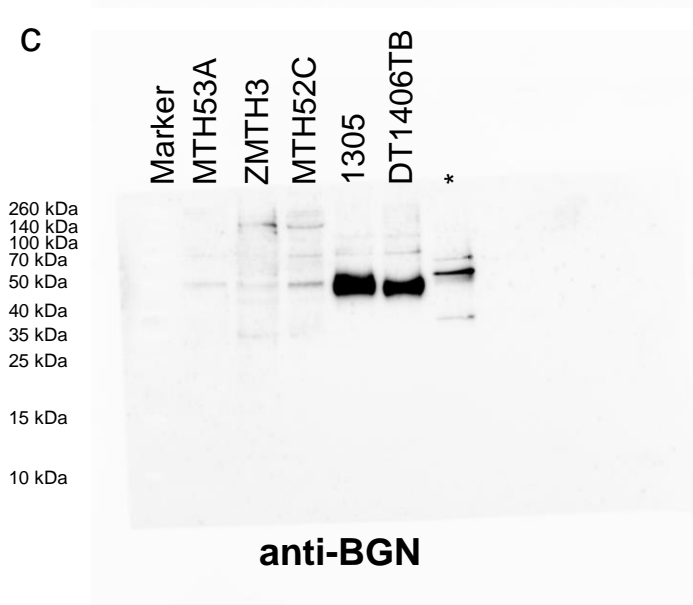
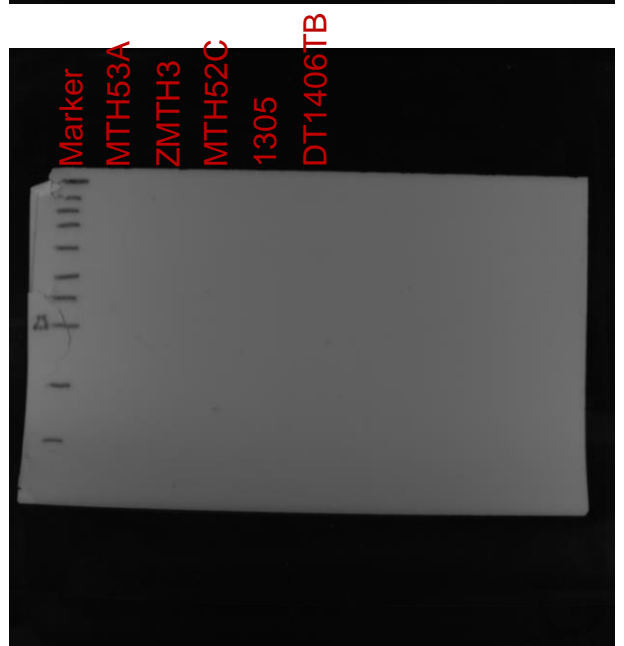
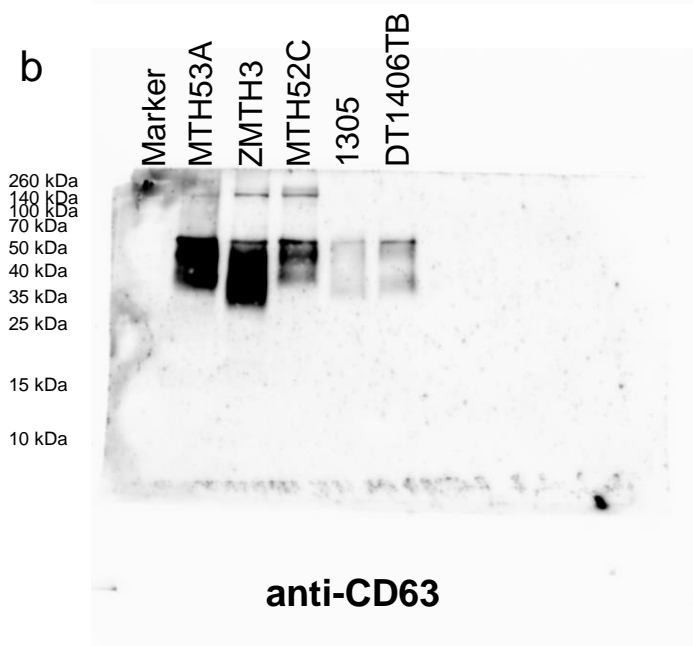
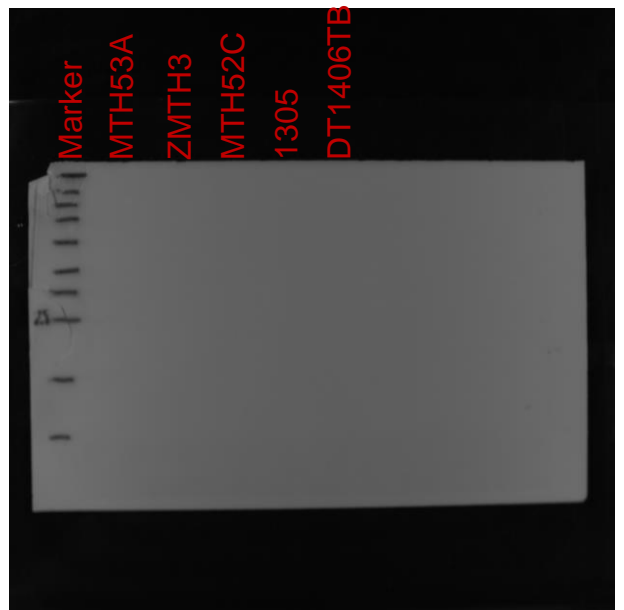
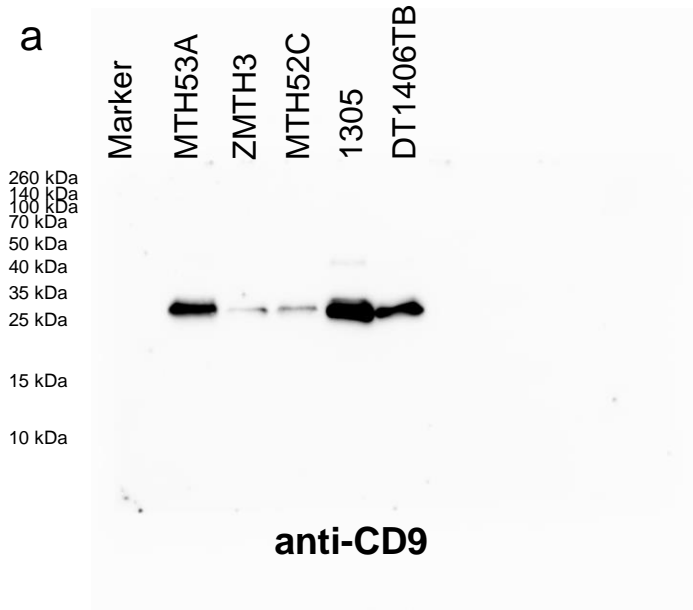
Additional file 9. WGCNA analysis. Identification of modules associated with traits of CMT. **a)** Sample clustering through dendrogram and trait heatmap. Samples were clustered and carcinoma samples grouped in simple carcinoma and complex carcinoma, and traits were subdivided to differentiate WCL and EV-derived protein. **b)** Correlation of module traits. Red represented a positive correlation, while blue represented a negative correlation. **c)** Trait dendrogram and module colours. Clustered proteins were selected into module colours according to the co-abundance of proteins in each sample.



Additional file 10. Western blot of EV proteins for BGN. Samples were de-glycosylated with chondroitinase ABC for 16 hours at 37°C prior to western blotting. EV proteins were then separated by SDS-PAGE and incubated with an anti-BGN antibody as described in Materials and Methods. Images were acquired after 5 minutes of exposure using a Fusion imaging system. The image shows the strong over-representation of BGN in the two complex carcinoma cell lines 1305 and DT1406TB.



Additional file 11. Immunofluorescence of our cell lines for BGN protein **a)** MTH53A, **b)** ZMTH3, **c)** MTH52C, **d)** 1305, **e)** DT1406TB. Images were acquired with a 40x objective under identical exposure settings.



* whole cell lysate of DT1406TB not used in this study

Additional file 12. Original unprocessed images (luminescence left; brightfield on the right) of western blots shown in Additional file 5 (**a**) CD9, **b**) CD63) and Additional file 10 (**c**) BGN). Images were acquired after 5 minutes of exposure using a Fusion imaging system (default settings).

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