ID	Histological group	CS	ZN	Anti-Map ELISA	PCR feces	PCR tissues	Culture feces	Culture tissues	Age (years)
ANIMALS WITH DIFFUSE MULTIBACILLARY LESIONS									
1	Diffuse	YES	POS (+++)	POS (157.83)	POS	POS	POS (>50)	POS (>50)	4.82
2	Diffuse.	YES	POS (+++)	POS (155.82)	POS	POS	NEG	POS (>50)	10.39
3	Diffuse	YES	POS (+++)	POS (215.95)	POS	POS	NEG	POS (>100)	4.74
4	Diffuse	YES	POS (+++)	POS (242.36)	POS	POS	POS (>100)	POS	5.82
5	Diffuse	YES	POS (+++)	POS (174.43)	INC	POS	POS	POS	6.70
6	Diffuse	YES	POS (+++)	POS (169.16)	POS	POS	NEG	POS (10-50)	6.70
7	Diffuse	YES	POS (+++)	POS (208.82)	POS	POS	POS (<10)	POS (>100)	5.35
8	Diffuse	YES	POS (+++)	POS (214.95)	POS	POS	POS (10-50)	POS (50-100)	6.48
ANIMALS WITH MULTIFOCAL LESIONS									
9	Multifocal	NO	POS (++)	POS (67.58)	POS	POS	POS (<10)	POS (>50)	5.51
10	Multifocal	NO	NEG (-)	NEG (2.96)	NEG	POS	NEG	POS (10-50)	4.03
11	Multifocal	NO	POS (+)	NEG (1.5)	NEG	NEG	NEG	POS (<10)	7.31
12	Multifocal	NO	POS (+)	POS (148.65)	POS	POS	NEG	NEG	5.65
13	Multifocal	NO	POS (+)	NEG (3.34)	NEG	NEG	NEG	NEG	5.58
14	Multifocal	NO	POS (+)	NEG (3.46)	INC	POS	NEG	NEG	7.70
15	Multifocal	NO	POS (+)	NEG (12.56)	POS	POS	POS (>50)	NEG	6.14
16	Multifocal	NO	POS (+)	NEG (3.41)	POS	NEG	NEG	POS (10-50)	2.57
17	Multifocal	NO	POS (+)	NEG (4.58)	INC/NEG	POS	NEG	NEG	10.39
18	Multifocal	NO	POS (+)	NEG (13.72)	INC/POS	POS	NEG	NEG	5.39
19	Multifocal	NO	POS (+)	POS (68.86)	NEG	NEG	NEG	NEG	5.34
20	Multifocal	NO	POS (++)	NEG (1.65)	NEG	NEG	NEG	NEG	4.25
21	Multifocal	NO	POS (+)	NEG (4.57)	NEG	NEG	NEG	NEG	4.50
22	Multifocal	NO	POS (+)	NEG (5.06)	NEG	POS	NEG	NEG	7.31
CONTROL ANIMALS WITH NO VISIBLE LESIONS									
23	No lesions	NO	NEG (-)	NEG (2.45)	NEG	INC	NEG	NEG	1.27
24	No lesions	NO	NEG (-)	NEG (1.26)	NEG	NEG	NEG	NEG	2.70
25	No lesions	NO	NEG (-)	NEG (5.44)	NEG	NEG	NEG	NEG	3.26
26	No lesions	NO	NEG (-)	NEG (8.84)	NEG	NEG	NEG	NEG	0.81
27	No lesions	NO	NEG (-)	NEG (18.37)	NEG	NEG	NEG	NEG	8.25
28	No lesions	NO	NEG (-)	NEG (2.91)	NEG	NEG	NEG	NEG	4.62
29	No lesions	NO	NEG (-)	NEG (2.95)	NEG	NEG	NEG	NEG	3.20

Supplementary Table 1. Infectious status of the animals (n=29) used for the proteomic analysis of sera and ileocecal valve (ICV).

ID, cows identification; INC, inconclusive result after repeating the analyses twice; CS, clinical signs; ZN, Ziehl–Neelsen; Diffuse, refers to animals with diffuse multibacillary histological lesions; The +, ++ and +++, indicate the abundance of acid-alcohol resistant bacteria; For the positive results in the bacteriological cultures, the number of positive colonies is indicated in parenthesis; For the anti-Map ELISA, the result (positive and negative) and the numerical value (percentage of the sample (S)/positive control (P) ratio) obtained in the ELISA are indicated. The cut off value of the ELISA is 55% (S/P ≥55% positive sample). Age refers to the age at which the animals died or were sacrificed due to PTB, accidents in the farm, or other diseases. CS registered were presence of diarrhoea, loss of weight/cachexia, and decreased production of milk. To consider that one animal had clinical signs, it had to present at least two of them.

ID	GROUP	ZN		ELISA IDEXX	ELISA IDEXX (number value)	PCR FECES	PCR TISSUES	CULTURE FECES	CULTURE TISSUES	AGE (YEARS)	CLINICAL SIGNS	ABCC4 (ng/mL)	GART (ng/mL)	GSS (ng/mL)	HBB (ng/mL)	PGK1 (ng/mL)	SCP2 (ng/mL)	SERPIN A3-3 (ng/mL)	IMPA-1 (pg/mL)
1	D.I.	POS	++	POS	137.1	POS	POS	NEG	POS	8.4	YES		0	102	6883.3	160	825.4	0	0
2	D.I.	POS	++	NEG	4.6	NEG	NEG	NEG	NEG	4.9	NO	86.1	0	74.5	3738.9	277.5	736.8	0	0
3	D.I.	POS	++	NEG	41.6	NEG	NEG	NEG	NEG	2.2	NO	89.1	0	49	1527.8	215.4	548.6	0	0
4	D.I.	POS	++	POS	205.9	POS	POS	NEG	POS	5.2	YES	97.4	43.9	146.3	10039	293.1	712.2		
5	D.I.	POS	+	POS	187.7	POS	POS	NEG	POS	5.5	NO	88	0	55.7	1327.8	304.4	473.6	0	0
6	D.I.	POS	+	POS	241.2	POS	POS	POS	POS	4.5	YES	74.2	2.1	57	2238.9	210.7	470.9	1.8	74.1
7	D.I.	POS	++	POS	113.5	POS	POS	NEG	NEG	5.1	YES	39.1	1	24.2	1683.3	356.6	578.6	0.7	8
8	D.I.	POS	+	POS	211.4	POS	POS	NEG	POS	4.9	NO	78	6.2	28.9	3772.2	345.1	670	5.2	87.9
9	D.I.	POS	++	POS	56.7	POS	POS	NEG	POS	6.2	YES	78	0.6	66.4	4983.3	231.8	871.8	0	0
10	D.I.	POS	++	POS	210.8	POS	POS	NEG	NEG	3.9	YES		0.5	99.3	1694.4	124.9	525.4	1.7	136.1
11	D.I.	POS	++	POS	193	POS	POS	POS	POS	6.4	YES	80.6	0	60.4	1138.9	91.3	454.5	0	0
12	D.I.	POS	++	POS	122.7	POS	NC	NEG	NEG	3.4	YES	65.5	0.7	71	750	20.4	326.2	0	0
13	D.L.	POS	+	NEG	9.5	NC	POS	NEG	NEG	8	NO	40.9	1	150.8	7807.1	171.4	232	32.7	42.2
14	D.M.	POS	+++	POS	286.5	POS	POS	NEG	POS	2.9	YES	79.2	0	77.2	1672.2	33.9	589.5	0	0
15	D.M.	POS	+++	POS	174.4	NC	POS	POS	POS	6.7	YES	63.6	0.9	128.9	4991.4	101.3	469.5	4	21.1
16	D.M.	POS	+++	POS	157.8	POS	POS	POS	POS	4.8	YES	72.6	0	93.3	2927.8	200.1	466.8	0	0
17	D.M.	POS	+++	POS	242.4	POS	POS	POS	POS	5.8	YES		1.4	262.4	10250	112.9	1795	7.7	919.1
18	D.M.	POS	+++	POS	155.8	POS	POS	NEG	POS	10.4	YES	72.6	0.2	87.9	4038.9	113.5	536.3	0	0
19	D.M.	POS	+++	POS	215.9	POS	POS	NEG	POS	4.7	YES	63.3	0	34.9	427.8	11.6	376.8	0	0
20	D.M.	POS	+++	POS	169.2	POS	POS	NEG	POS	6.7	YES	76.3	3.3	36.5	1021.4	49.9	197.9	0	0
21	D.M.	POS	+++	POS	215	POS	POS	POS	POS	6.5	YES	67.5	1.1	38.2	821.4	68.1	310.7	0	0
22	D.M.	POS	+++	POS	208.8	POS	POS	POS	POS	5.4	YES	84.1	0.7	45	21.4	172.7	332.4	0	0

23	Focal	POS	+	NEG	6.6	NEG	POS	NEG	NEG	8.6	NO	48.9	0	31.5	916.7	86.2	382.2	0	0
24	Focal	POS	+	NEG	10.9	NEG	NEG	POS	NEG	6.6	NO	80.4	4.1	114.8	4794.4	131.9	682.2	6.2	544.1
25	Focal	POS	+	NEG	4.1	NEG	NEG	NEG	NEG	4	NO	48.6	2.4	108.7	5272.2	108.1	712.2	2.6	286.7
26	Focal	POS	+	NEG	17.3	NEG	NEG	NEG	NEG	4.3	NO	76.6	0	67.1	4650	213.6	468.1	0	175.3
27	Focal	NEG		POS	157.8	NC	NEG	NEG	POS	8.3	NO	72.3	43.7	40.9	3394.4	208.5	903.1		3521.7
28	Focal	POS	+	NEG	4.5	NEG	NEG	NEG	NEG	5.4	NO	42.2	0	22.8	2861.1	346	320.9	0	0
29	Focal	POS	+	NEG	9.3	NEG	NEG	NEG	NEG	2.6	NO	99.3	0	102	1683.3	103.2	735.4	0	0
30	Focal	POS	+	NEG	33.2	NEG	NEG	NEG	NEG	5.9	NO	72.8	0.2	102.7	5294.4	311.2	800.9	0.3	0
31	Focal	POS	+	NEG	10	NEG	NEG	NEG	NEG	6.1	NO	55.7	0.1	145.6	7827.8	283.6	498.1	0	0
32	Focal	POS	+	NEG	5.4	NEG	NEG	NEG	NEG	12.7	NO	62.1	0	51.7	938.9	43.2	314	0	0
33	Focal	POS	+	NEG	6.5	NEG	NEG	NEG	NEG	6.8	NO	109.5	0.7	95.3	5683.3	126.3	1008	0.6	12.5
34	Focal	POS	+	NEG	0.6	NEG	NEG	NEG	NEG	4.2	NO	84.4	0.5	161.1	4061.1	276	740.9	0	0
35	Focal	NEG		NEG	6.8	NEG	POS	NEG	POS	4.1	NO	47.9	0	55.7	1527.8	287.5	350.9	0	0
36	Focal	POS	+	NEG	3.4	NEG	POS	NEG	NEG	7	NO	40.1	0	1188.6	26717	347	485.9	2.3	0
37	Focal	POS	+	NEG	3.1	NC	POS	NEG	NEG	8.4	NO	26.6	1.1	94.6	4138.9	242.2	117.7	0.1	0
38	Focal	POS	+	NEG	11.8	NEG	NEG	NEG	NEG	5.4	NO	86.5	0	14.1	172.2	286	499.5	0	0
39	Focal	POS	+	NEG	4.2	POS	POS	NEG	POS	6.3	NO	60.9	0	60.4	994.4	309.5	360.4	0	0
40	Focal	POS	+	NEG	1.2	NEG	NEG	NEG	NEG	5.2	NO	64	0	55.7	716.7	178	421.8	0	0
41	Focal	POS	+	NEG	2.8	POS	NEG	POS	NEG	4.5	NO	63.6	0	102.7	1327.8	113.8	406.8	0	0
42	Focal	POS	+	NEG	10	NEG	NEG	NEG	NEG	4.3	NO	86.1	0	343	7761.1	206.2	828.1	0	0
43	Focal	POS	+	NEG	7.9	NEG	POS	NEG	POS	7.4	NO	106.2	0	304	9372.2	355.6	777.7	0	0
44	Focal	NEG		NEG	4	POS	NEG	NEG	NEG	2.9	NO	96	0	46.3	727.8	161.4	454.5	0	0
45	Focal	POS	+	NEG	2.7	NEG	POS	NEG	POS	4.7	NO	79	0	20.8	283.3	228.7	476.3	0	0
46	Focal	NEG		NEG	0.8	POS	POS	NEG	POS	8.4	NO	73.5	0	53	1116.7	334.9	398.6	0	0
47	Focal	POS	+	NEG	11.7	NEG	NEG	NEG	NEG	8.2	NO	109.1	0	115.8	2478.6	50.6	473.1	0	0
48	Focal	NEG		NEG	1	NEG	POS	NEG	POS	7.2	NO	74.4	1.5	63.4	807.1	211.8	390.3	1.4	77.8
49	Focal	NEG		NEG	6.2	NEG	NEG	NEG	POS	5.5	NO	74	0.6	36.9	192.9	48	306.5	0	0
50	Focal	POS	+	NEG	2.8	NEG	POS	NEG	NEG	9.5	NO	33.4	1.1	28.4	335.7	157.6	242.4	0	0

51	Focal	NEG		NEG	0.7	NEG	POS	NEG	NEG	6.8	NO	104.5	0.5	57.8	2527.8	118.4	599.3	0	0
52	Focal	POS	+	NEG	3.8	NEG	NEG	NEG	NEG	4.4	NO	59.3	0.8	25.8	707.1	74.2	260	0	0
53	Focal	POS	+	NEG	1.1	NEG	NEG	NEG	POS	4.4	NO	48.3	0.7	63.8	3850	43	429.6	0	0
54	Focal	POS	+	NEG	1.5	NEG	POS	NEG	NEG	6.5	NO	43.7	0.7	45	0	243.5	158.6	0	0
55	Focal	POS	+	NEG	0.1	NC	POS	NEG	NEG	5.9	NO	42.3	0.6	83.4		182.5	252.7	0	0
56	Focal	POS	+	NEG	5.1	NEG	POS	NEG	NEG	5.9	NO	70.5	1.1	88.1	2592.9	22.8	367.6	0.6	0
57	Focal	NEG		NEG	37.2	NEG	NEG	NEG	POS	3	NO	68.2	0.6	257.4	12121	143.5	320	0	0
58	Focal	NEG		NEG	3.8	POS	POS	POS	POS	2.6	NO	54.9	0.8	24.6	1135.7	100.7	268.2	0	185.2
59	Focal	POS	+	NEG	14.3	POS	POS	NEG	NEG	4	NO	58.6		37.8	1492.9	52.2	396.5	2.7	340.7
60	Focal	NEG		NEG	2.4	NEG	NEG	NEG	POS	1.3	NO	60.7	3.9	25.8	1121.4	133.8	309.6	0	0
61	Focal	POS	+	NEG	1.9	NC/POS	POS	NEG	NEG	6	NO	61.6	1.2	24.6	1278.6	31	215.5	0.1	0
62	Focal	POS	+	NEG	2.4	NEG	NEG	NEG	POS	2.1	NO	52.4	1.3	56.5	1092.9	31	342.7	0	0
63	Focal	POS	+	NEG	7.4	POS	POS	NEG	NEG	5.9	NO	108.1	1.1	188.7	8492.9	32.4	624.1	0	23.4
64	Focal	POS	+	NEG	1.5	POS	POS	NEG	NEG	3.4	NO	100.8	0.7	97.1	5850	77.9	462.7	17.9	813.4
65	Focal	POS	+	NEG	4	POS	NEG	NEG	NEG	4.2	NO	202.6	26.7	133.3		64.6	1412	0.6	0
66	Focal	POS	+	NEG	3.4	NEG	POS	NEG	POS	4.7	NO	58.8	1.1	31.8	892.9	200.4	330.3	1.4	2.5
67	Focal	POS	+	NEG	7.6	NEG	POS	NEG	NEG	4.5	NO	74	2.2	22.9	507.1	82.3	261	0.4	0.4
68	Focal	NEG		NEG	15.3	NC	NEG	NEG	NEG	5.4	NO	52.6	1.2	28.8	1050	321.1	185.5	0	0
69	Focal	NEG		NEG	10.6	NEG	NEG	NEG	NEG	8.7	NO	61.8	0.8	75.3		303.1	257.9	0	0
70	M.F.	POS	+	NEG	6.6	NC	NEG	NEG	POS	6.6	NO	96.5	0.2	43.6	2394.4	204.5	712.2	0	0
71	M.F.	POS	+	POS	68.9	NEG	NEG	NEG	NEG	5.3	NO	43.6	0	564.4	18906	278.3	619.5	2.3	0
72	M.F.	POS	+	POS	148.7	POS	POS	NEG	NEG	5.7	NO	64.1	0.6	183.6	5135.7	470.7	713.1	0	0
73	M.F.	POS	+	NEG	3.3	NEG	NEG	NEG	NEG	5.6	NO	94.6	0.6	94.1	4535.7	271.4	650	28.4	811.2
74	M.F.	POS	+	NEG	3.4	NC	NEG	NEG	NEG	6.6	YES	71.4		48.9	2207.1	138.7	359.3	1.1	0
75	M.F.	POS	+	NEG	4.5	POS	POS	NEG	NEG	3.3	YES	88	1.6	22.4	978.6	96.2	579.6	0.2	251
76	M.F.	POS	+	NEG	3.1	NEG	POS	NEG	NEG	2.5	YES	95.5	2	47.6	5035.7	90	515.5	6.7	422.4
77	M.F.	POS	+	NEG	3.2	NEG	NEG	NEG	NEG	6.6	NO	97.4	16.4	47	1505.6	148.7	728.6	0	0
78	M.F.	POS	+	NEG	1.5	NEG	NEG	NEG	POS	7.3	NO	51.2	0	36.2	1183.3	10.4	394.5	0	0

79	M.F.	POS	++	POS	67.6	POS	POS	POS	POS	5.5	NO	102.4	0	36.2	672.2	8.1	428.6	0	0
80	M.F.	POS	+	NEG	4.8	NEG	NEG	NEG	POS	9.7	NO	48.9	0	34.2	1361.1	81.4	293.6	0.4	0
81	M.F.	POS	+	NEG	12.6	POS	POS	POS	NEG	6.1	NO	57.2	0	28.2	927.8	69	349.5	1.4	0
82	M.F.	POS	+	NEG	4.6	NC/NEG	POS	NEG	NEG	10.4	NO	84.6	0.5	27.5	1261.1	286	603.1	0.2	0
83	M.F.	POS	+	NEG	7.6	NEG	NEG	NEG	NEG	6.4	NO	120.9	0	104.7	7672.2	159.6	1050	4.8	284.4
84	M.F.	POS	+	NEG	3.5	NC	POS	NEG	NEG	7.7	NO	86.4	2.6	13.5	278.6	16.7	296.2	0	0
85	M.F.	POS	+	NEG	4.9	NEG	POS	NEG	NEG	5.7	NO	59.3	0.9	283.8	17321	219.1	369.6	25.5	1237.1
86	M.F.	POS	+	NEG	13.7	NC/POS	POS	NEG	NEG	5.39	NO	22.3	33.9	41.6	2683.3	372.5			0
87	M.F.	POS	+	NEG	5.1	NEG	POS	NEG	NEG	7.3	NO	111.1	4.3	173.8	8235.7	143.1	480.3	0	0
88	M.F.	NEG		NEG	3	NEG	POS	NEG	POS	4	NO	50.3	1.4	50.6	1835.7	157.2	211.3	0	0
89	M.F.	POS	+	NEG	3.1	NEG	NEG	NEG	NEG	4.1	NO	29.9	0.6	39.1	2607.1	276	304.4	0	0
90	M.F.	POS	+	NEG	1.7	NEG	NEG	NEG	NEG	4.3	NO	77.9		10.5	707.1	42.3	500	0	0
91	M.F.	POS	+	NEG	4.6	NEG	NEG	NEG	NEG	4.5	NO	51.7	0.6	144.8	13493	194.7	246.5	3	0
92	M.F.	POS	+	NEG	3.4	POS	NEG	NEG	POS	2.6	NO	49.7	1.2	26.3	1764.3	62	371.7	1.9	113.5
93	M.F.	POS	+	NEG	2.2	NEG	NC/POS	NEG	NEG	4.6	NO	66.4	2	38.2	1178.6	24.2	338.6	0.5	54.7
94	M.F.	POS	+	NEG	2.1	NC	NEG	NEG	NEG	4.8	NO		0.7	67.1	3507.1	334.9		0	0
95	PTB-F.F			NEG	3.2	NEG		NEG		4.5	NO	69.2	0	73.8	838.9	114.5	380.9	0.1	0
96	PTB-F.F			NEG	9.2	NEG		NEG		7.6	NO	79.9		39.6	1183.3	88.1	573.1	2.1	0
97	PTB-F.F			NEG	1.3	NEG		NEG		3.3	NO	56.4		59.1	2227.8	49.3	348.1	0	0
98	PTB-F.F			NEG	5.5	NEG		NEG		3.5	NO	81.6	0	69.1	2194.4	52.4	344	1	0
99	PTB-F.F			NEG	1.8	NEG		NEG		3.8	NO	80.4	0.3	28.2	561.1	76.5	349.5	0.2	0
100	PTB-F.F			NEG	0.6	NEG		NEG		3.7	NO	69.2	0.1	37.6	2327.8	52.5	390.4	0	0
101	PTB-F.F			NEG	4.4	NEG		NEG		4.3	NO	32	0	20.8	605.6	220.7	400	0	0
102	PTB-F.F			NEG	4.4	NEG		NEG		3.9	NO	50.8	0	26.2	916.7	286	265	0.3	0
103	PTB-F.F			NEG	11.1	NEG		NEG		10.1	NO	65.9	0	48.3	1227.8	69.1	329	0	0
104	PTB-F.F			NEG	3.3	NEG		NEG		9.8	NO	74	0	38.9	283.3	85.3	477.7	0	0
105	PTB-F.F			NEG	0.2	NEG		NEG		3.9	NO		0	110.1	3283.3	51.8	922.2	0	0

106	PTB-F.F			NEG	4	NEG		NEG		5.8	NO	57.2	0	18.1	227.8	164.9	308.6	0	0
107	PTB-F.F			NEG	20.3	NEG		NEG		5.7	NO	65	0	56.4	1450	106.9	532.2	12.6	347.5
108	PTB-F.F			NEG	4.3	NEG		NEG		3.3	NO		5.2	49	838.9	84.1	483.1	0	0
109	PTB-F.F			NEG	9.7	NEG		NEG		4.7	NO	59.1	0.1	35.6	805.6	108.7	404	0.1	0
110	PTB-F.F			NEG	2.8	NEG		NEG		3.8	NO	62.4	0.1	52.3	1438.9	96.1	228.1	5.4	371
111	PTB-F.F			NEG	13.9	NEG		NEG		4.8	NO	86.8	1.5	45.6	738.9	134.4	288.1	0	0
112	PTB-F.F			NEG	2.8	NEG		NEG		6.4	NO	49.1	0	127.5	5105.6	69.5	267.7	20.9	1329.2
113	PTB-F.F			NEG	3.3	NEG		NEG		3.3	NO	59.8	6.4	79.2	3005.6	123.5	278.6		2939.3
114	PTB-F.F			NEG	7.3	NEG		NEG		3.6	NO	80.4	39.7	109.4	4750	175.1	668.6	4.8	0
115	PTB-F.F			NEG	12.7	NEG		NEG		4.7	NO	63.8	3.4	42.3	1027.8	245.5	582.7	0	0
116	PTB-F.F			NEG	4.4	NEG		NEG		7	NO	71.4	0	57	1661.1	119.9	344	4.4	147.6
117	PTB-F.F			NEG	16.4	NEG		NEG		9.1	NO	53.6	2.9	45	738.9	107.2	245.9	0	0
118	PTB-F.F			NEG	6.9	NEG		NEG		4.5	NO	81.3	0	85.2	1750	138.5	567.7	0	0
119	PTB-F.F			NEG	20.8	NEG		NEG		4.5	NO	82.5	0	67.2	2035.7	80.9	448.2	0	0
120	PTB-F.F			NEG	10.1	NEG		NEG		4.3	NO	71.9	2.3	30.1	807.1	153.1	416.2	0	0
121	PTB-F.F			NEG	-0.3	NEG		NEG		4.2	NO	57.2	1.2	49.7	11250	136.1	494.8	2.5	223.3
122	PTB-F.F			NEG	14.9	NEG		NEG		3.1	NO		6.8	125.2	3021.4	110.9	1643	1.3	0
123	PTB-F.F			NEG	1.1	NEG		NEG		9.9	NO	40.9	1	17.7	2078.6	112.3	265.1	0.3	0
124	PTB-F.F			NEG	9.8	NEG		NEG		2.6	NO		2.5	297.5	16528	128.4	3066	1.6	0
125	PTB-F.F			NEG	10.3	NEG		NEG		2.3	NO		1.3	48.9		207.8	1261	9	334.2
126	PTB-F.F			NEG	7.6	NEG		NEG		2.8	NO		1.9	114.5		113.9	790.7	0	0
127	PTB-F.F			NEG	13.1	NEG		NEG		5.3	NO	63.4	9.4	25.8		111.7	241.3	0.3	0
128	PTB-F.F			NEG	2.6	NEG		NEG		2.3	NO	71.7	1.4	38.2		165.7	355.1	7.1	387.9
129	PTB-F.F			NEG	4.9	NEG		NEG		2.5	NO	46.9	6.2	36.1		192.4	422.4	0	0
130	PTB-F.F			NEG	6	NEG		NEG		2.3	NO	74	1	29.3		98.8	524.8	3.3	274.4
131	PTB-F.F			NEG	2.1	NEG		NEG		2.3	NO	51.5	2.9	26.3		54.6	265.1	1	126.1
132	PTB-F.F			NEG	3.7	NEG		NEG		4.5	NO		3.2	80.4		81.9	1219	1.5	0
133	PTB-F.F			NEG	4.4	NEG		NEG		2.6	NO	34.7	2.3	51.9		144.9	283.8	0	0

134	PTB-F.F			NEG	12.8	NEG		NEG		2.5	NO	58.6	1.2	81.7		187.4	262	0	0
135	PTB-F.F			NEG	7.2	NEG		NEG		6.9	NO	58.4	0.6	40.3		59.9	321	0.2	0
136	PTB-F.F			NEG	5.7	NEG		NEG		7.3	NO		1	33.1		60.6	478.2	0	0
137	PTB-F.F			NEG	7.5	NEG		NEG		1.8	NO	60.9	1.6	54		175.2	231	0.5	0
138	PTB-F.F			NEG	0.1	NEG		NEG		0.7	NO			124.3		129.1	946.9		
139	PTB-F.F			NEG	0.2	NEG		NEG		1.3	NO	86.3	34.3						0
140	W.L.	NEG		NEG	5.4	NEG	NEG	NEG	NEG	3.3	NO		0			352.7			
141	W.L.	NEG		NEG	18.4	NEG	NEG	NEG	NEG	8.3	NO	68.3	0						0
142	W.L.	NEG		NEG	1.7	NEG	NEG	NEG	NEG	3.6	NO	70.9	6.3	287.2	13294	161.8	949.5	33.1	720.2
143	W.L.	NEG		NEG	2.5	NEG	NC	NEG	NEG	1.3	NO	67.1	36.8	100	4305.6	92.5	746.3	0.6	177.6
144	W.L.	NEG		NEG	2.9	NEG	NEG	NEG	NEG	4.6	NO	69.8	0.2	30.2	1127.8	226.2	550	0	
145	W.L.	NEG		NEG	3	NEG	NEG	NEG	NEG	3.2	NO	49.2		51.9	1592.9	118.9	387.2	0.5	2.5
146	W.L.	NEG		NEG	-4.9	NEG	NEG	NEG	NEG	1	NO	80.6	1.3	45	135.7	16.8	324.1	0	0

Supplementary Table 2. Infectious status and age and serum concentration values of ABCC4, GART, GSS, HBB, IMPA1, PGK1, SCP2, SERPIN A3-3, differentially expressed proteins (DEPs) of the animals used for pre-validation of the proteomic analysis results.

ABCC4, ATP Binding Cassette Transporter C4; GART, Glycinamide ribonucleotide synthetase, isoform 2; GSS, Glutathione Synthetase; HBB, Bovine Haemoglobin subunit Beta; IMPA1, Inositol Monophosphatase 1; PGK1,Phosphoglycerate Kinase 1; SCP2, Non-specific lipid-transfer protein; and SERPINA3-3; The concentration of the differentially expressed selected proteins is given in ng/mL but for IMPA1 that is given in pg/mL.The concentration was determined using commercial bovine DE-proteins specific ELISAs. D.I., diffuse intermediate; D.L., diffuse lymphocytic; D.M., diffuse multibacillary. NC, inconclusive result. IMPA1 and SERPIN A3-3 levels below the assay detection limit were considered zero. The analytical sensitivity of the ELISAs was 15.2 pg/mL and 0.1 ng/mL, respectively.

COMPARISON	term ID	term description	Gene count	B-gene count	ST	S	FDR	matching proteins (labels)
Diffuse Animals Versus No- lesion Control	CL:3020	RNA recognition motif domain, and DZF domain	8	55	1.18	0.88	1.31e-05	SYNCRIP,NONO,HNRNPK,HNRNPA3,SRSF7,SRSF1,PCBP2,HNRNPD
	CL:16669	Mixed, incl. Extracellular matrix organization, and ECM-receptor interaction	12	174	0.86	0.78	1.03e-05	TNXB,COL14A1,COL6A2,FLNB,COL1A2,ITGA1,VCL,ITGB2,TNS1,VCAN,RSU1,FBLN1
	CL:2252	Protein folding, and Cellular response to unfolded protein	9	140	0.83	0.59	0.00024	TCP1,HSP90AA1,CCT7,CCT6B,HSPA8,HSPA2,TXNDC5,HSPE1,CCT6A
	CL:9706	Carbon metabolism, and Pyruvate metabolism	11	123	0.97	0.83	0.00029	PGK1,TKT,MDH2,TALDO1,ENO1,PGAM2,IDH1,FH,H6PD,SDHB,MPST
	CL:3021	Mixed, incl. mRNA Processing, and DZF domain	7	47	1.19	0.82	0.00057	SYNCRIP,HNRNPK,HNRNPA3,SRSF7,SRSF1,PCBP2,HNRNPD
	CL:3026	mRNA Processing, and Viral RNA genome replication	6	28	1.35	0.85	0.00057	HNRNPK,HNRNPA3,SRSF7,SRSF1,PCBP2,HNRNPD
	CL:35224	Mixed, incl. P-type trefoil, chordata, and Lung goblet cell differentiation	5	15	1.54	0.87	0.00058	FCGBP,CLCA1,AGR2,TFF2,REG4
	CL:2260	Unfolded protein binding, and Protein folding	8	95	0.95	0.66	0.0020	TCP1,HSP90AA1,CCT7,CCT6B,HSPA8,HSPA2,HSPE1,CCT6A
	CL:9714	Glycolysis, and Transketolase or transaldolase activity	5	23	1.36	0.72	0.0020	PGK1,TKT,TALDO1,ENO1,PGAM2
	CL:10171	Alpha-amino acid metabolic process, and One carbon pool by folate	8	111	0.88	0.58	0.0040	ADSL,PHGDH,SQOR,ALDH18A1,AHCY,ATIC,SELENBP1,ENSBTAP00000072240
	CL:16857	Mixed, incl. ECM-receptor interaction, and Cell-extracellular matrix interactions	7	80	0.96	0.6	0.0040	TNXB,FLNB,ITGA1,VCL,ITGB2,TNS1,RSU1
	CL:2408	Chaperone tailless complex polypeptide 1 (TCP-1)	4	13	1.51	0.65	0.0040	TCP1,CCT7,CCT6B,CCT6A
	CL:472	Cytoplasmic ribosomal proteins, and Cytoplasmic side of rough endoplasmic reticulum membrane	6	53	1.08	0.61	0.0041	RPS17,RPS9,RPL11,RPS7,RPL35,RPL5
	CL:9832	Tricarboxylic acid cycle, and Aspartate metabolic process	5	32	1.22	0.61	0.0045	MDH2,IDH1,FH,SDHB,MPST
	CL:9709	Pentose phosphate pathway, and Glycolytic process	6	57	1.04	0.58	0.0051	PGK1,TKT,TALDO1,ENO1,PGAM2,H6PD

	CL:9716	Glycolysis, and Transketolase or transaldolase activity	4	16	1.42	0.61	0.0053	PGK1,TKT,TALDO1,ENO1
	CL:3027	Mixed, incl. Zinc finger, CHHC-type, and Heterogeneous nuclear ribonucleoprotein A1/A2, C-terminal	4	17	1.39	0.59	0.0063	HNRNPK,HNRNPA3,PCBP2,HNRNPD
	CL:37695	MHC class I protein complex assembly, and Beta-2-Microglobulin	3	5	1.8	0.61	0.0064	CALR,TAPBP,PDIA3
	CL:35226	Mixed, incl. Lung goblet cell differentiation, and Proteinase inhibitor I1, Kazal-type, metazoa	3	6	1.72	0.56	0.0092	FCGBP,CLCA1,AGR2
	CL:25355	RHO GTPases Activate WASPs and WAVEs, and Regulation of actin polymerization or depolymerization	6	73	0.94	0.48	0.0126	ARPC4,CORO1C,GSN,CORO1B,E1BHJ0_BOVIN,ACTR3
	CL:25357	Arp2/3 protein complex, and Negative regulation of actin nucleation	4	23	1.26	0.5	0.0130	ARPC4,CORO1C,CORO1B,ACTR3
	CL:460	GTP hydrolysis and joining of the 60S ribosomal subunit, and Cytosolic ribosome	7	108	0.83	0.46	0.0130	RPS17,RPS9,RPL11,E1BK63_BOVIN,RPS7,RPL35,RPL5
	CL:2410	Chaperonin TCP-1, conserved site	3	8	1.6	0.51	0.0144	TCP1,CCT7,CCT6A
	CL:475	Cytoplasmic ribosomal proteins, and Polysomal ribosome	5	48	1.04	0.47	0.0154	RPS17,RPS9,RPL11,RPS7,RPL35
	CL:16967	Mixed, incl. Cell-extracellular matrix interactions, and Alpha-catenin/vinculin-like superfamily	4	25	1.23	0.48	0.0159	FLNB,VCL,TNS1,RSU1
	CL:3030	Mixed, incl. Viral nucleoprotein, and ROK, N-terminal	3	10	1.5	0.46	0.0213	HNRNPK,HNRNPA3,HNRNPD
	CL:479	Cytoplasmic ribosomal proteins, and Ribosomal protein S30	4	28	1.18	0.44	0.0213	RPS17,RPS9,RPL11,RPL35
	CL:25349	Mixed, incl. Regulation of actin polymerization or depolymerization, and Arp2/3 complex binding	7	124	0.77	0.41	0.0226	LCP1,ARPC4,CORO1C,GSN,CORO1B,E1BHJ0_BOVIN,ACTR3
	CL:22445	Myosin II filament, and Smooth Muscle Contraction	3	11	1.46	0.44	0.0244	MYH9,ACTA2,MYH10
	CL:4619	ATP synthesis, and ATP synthase, F0 complex, subunit B	3	11	1.46	0.44	0.0244	ATP5F1A,ATP5F1B,ATP5MF
	CL:20966	Complement and coagulation cascades, and Serpin superfamily, domain 2	5	69	0.88	0.34	0.0478	HRG,F2,CRP,LOC506828,SERPINA3-3
	CL:426	Cytosolic ribosome	8	194	0.64	0.32	0.0478	RPS17,RPS9,E1B8K9_BOVIN,RPL11,E1BK63_BOVIN,RPS7,RPL35,RPL5

Multifocal Animals Versus No-lesion Control	CL:16669	Mixed, incl. Extracellular matrix organization, and ECM-receptor interaction	21	174	1.04	2.01	2.15e-11	TNXB,P4HB,LAMC1,COL14A1,HSPG2,COL12A1,NID2, FLNB,FLNA,COL18A1,COL4A1,ITGB1,COL6A5,FLNC, COL15A1,ITGA6,LAMA4,RSU1,TLN1,ACTN1,PLEC
	CL:16857	Mixed, incl. ECM-receptor interaction, and Cell-extracellular matrix interactions	13	80	1.16	1.64	4.76e-08	TNXB,LAMC1,NID2,FLNB,FLNA,ITGB1,FLNC,ITGA6,LAMA4, RSU1,TLN1,ACTN1,PLEC
	CL:3018	RNA recognition motif domain, and DZF domain	12	68	1.2	1.62	8.91e-08	PSPC1,SYNCRIP,NONO,RBMX,SFPQ,HNRNPK,HNRNPA3, SRSF7,DDX17,PCBP2,HNRNPR,HNRNPH1
	CL:3020	RNA recognition motif domain, and DZF domain	10	55	1.21	1.39	1.36e-06	PSPC1,SYNCRIP,NONO,SFPQ,HNRNPK,HNRNPA3,SRSF7, PCBP2,HNRNPR,HNRNPH1
	CL:9706	Carbon metabolism, and Pyruvate metabolism	13	123	0.98	1.23	1.95e-06	PGK1,PGM2,ACO2,TALDO1,ENO1,PGAM2,PGLS,TPI1,IDH1, DLD,ALDOA,MDH1,ACO1
	CL:9709	Pentose phosphate pathway, and Glycolytic process	8	57	1.1	0.89	0.00022	PGK1,PGM2,TALDO1,ENO1,PGAM2,PGLS,TPI1,ALDOA
	CL:9714	Glycolysis, and Transketolase or transaldolase activity	6	23	1.37	0.94	0.00024	PGK1,TALDO1,ENO1,PGAM2,TPI1,ALDOA
	CL:16970	Cell-extracellular matrix interactions, and Talin, central	5	12	1.57	0.94	0.00029	FLNB,FLNA,FLNC,TLN1,ACTN1
	CL:16967	Mixed, incl. Cell-extracellular matrix interactions, and Alpha-catenin/vinculin-like superfamily	6	25	1.33	0.91	0.00031	FLNB,FLNA,FLNC,RSU1,TLN1,ACTN1
	CL:20964	Complement and coagulation cascades, and Serpin superfamily, domain 2	10	115	0.89	0.79	0.00036	AHSG,HRG,TF,CFB,SERPIND1,ITIH2,LOC506828,AMBP, FGB, CFH
	CL:9710	Glycolytic process, and Sugar-phosphatase activity	7	45	1.15	0.84	0.00042	PGK1,PGM2,TALDO1,ENO1,PGAM2,TPI1,ALDOA
	CL:3026	mRNA Processing, and Viral RNA genome replication	6	28	1.29	0.86	0.00044	HNRNPK,HNRNPA3,SRSF7,PCBP2,HNRNPR,HNRNPH1
	CL:3021	Mixed, incl. mRNA Processing, and DZF domain	7	47	1.13	0.83	0.00047	SYNCRIP,HNRNPK,HNRNPA3,SRSF7,PCBP2,HNRNPR, HNRNPH1
	CL:16861	Integrin complex, and Laminin IV	6	30	1.26	0.84	0.00054	LAMC1,NID2,ITGB1,ITGA6,LAMA4,PLEC
	CL:9716	Glycolysis, and Transketolase or transaldolase activity	5	16	1.45	0.86	0.00057	PGK1,TALDO1,ENO1,TPI1,ALDOA
	CL:3027	Mixed, incl. Zinc finger, CHHC-type, and Heterogeneous nuclear ribonucleoprotein A1/A2, C-terminal	5	17	1.42	0.83	0.00070	HNRNPK,HNRNPA3,PCBP2,HNRNPR,HNRNPH1
	CL:20962	Mixed, incl. Complement and coagulation cascades, and Lipoprotein particle	11	164	0.78	0.69	0.00077	AHSG,HRG,TF,CFB,LRP1,SERPIND1,ITIH2,LOC506828, AMBP, FGB,CFH

	CL:16858	Integrin complex, and Laminin, N-terminal	7	55	1.06	0.75	0.00089	TNXB,LAMC1,NID2,ITGB1,ITGA6,LAMA4,PLEC
	CL:20965	Complement and coagulation cascades, and Serpin superfamily, domain 2	9	106	0.88	0.71	0.00089	AHSG,HRG,TF,CFB,SERPIND1,ITIH2,LOC506828,FGB,CFH
	CL:16671	Collagen formation, and Microfibril	8	83	0.94	0.71	0.0011	P4HB,COL14A1,HSPG2,COL12A1,COL18A1,COL4A1, COL6A5,COL15A1
	CL:16679	Collagen biosynthesis and modifying enzymes	5	22	1.31	0.74	0.0015	COL14A1,COL18A1,COL4A1,COL6A5,COL15A1
	CL:20974	Mixed, incl. Fibrinolysis, and Serine protease inhibitor	5	24	1.27	0.69	0.0022	AHSG,HRG,TF,ITIH2,FGB
	CL:22445	Myosin II filament, and Smooth Muscle Contraction	4	11	1.51	0.7	0.0024	MYH9,MYL9,MYH10,MYH11
	CL:20966	Complement and coagulation cascades, and Serpin superfamily, domain 2	7	69	0.96	0.63	0.0027	AHSG,HRG,TF,SERPIND1,ITIH2,LOC506828,FGB
	CL:16675	Collagen biosynthesis and modifying enzymes, and Collagen type XI trimer	6	46	1.07	0.64	0.0028	COL14A1,COL12A1,COL18A1,COL4A1,COL6A5,COL15A1
	CL:16672	Collagen formation, and Microfibril	7	72	0.94	0.61	0.0033	COL14A1,HSPG2,COL12A1,COL18A1,COL4A1,COL6A5, COL15A1
	CL:20976	Fibrinolysis, and Cystatin-like domain	4	13	1.44	0.65	0.0037	AHSG,HRG,ITIH2,FGB
	CL:3115	NOPS, and Matrin-3, RNA recognition motif 1	3	5	1.73	0.58	0.0079	PSPC1,NONO,SFPQ
	CL:20968	Mixed, incl. Hemostasis, and Serine protease inhibitor	6	60	0.95	0.51	0.0093	AHSG,HRG,TF,SERPIND1,ITIH2,FGB
	CL:7082	DNA recombinase complex, and HMG box A DNA-binding domain, conserved site	3	6	1.65	0.54	0.0105	E1BMK2_BOVIN,F1MF42_BOVIN,SERPINB1
	CL:9735	NADH regeneration, and Peptidyl-cysteine S-trans-nitrosylation	3	6	1.65	0.54	0.0105	PGK1,ENO1,TPI1
	CL:11425	Glutathione metabolism, and Detoxification of Reactive Oxygen Species	6	69	0.89	0.44	0.0171	GSS,GSR,GSTP1-2,EPHX1,ANPEP,CAT
	CL:21520	Mixed, incl. Exopeptidase activity, and Cystatin domain	6	70	0.89	0.44	0.0180	ANXA4,NAALADL1,NPEPPS,DPP3,BREH1,DPEP1
	CL:11426	Glutathione metabolism	5	45	1.0	0.44	0.0202	GSS,GSR,GSTP1-2,EPHX1,ANPEP
	CL:11423	Mixed, incl. Glutathione metabolism, and Cell redox homeostasis	7	104	0.78	0.41	0.0208	GSS,GSR,GSTP1-2,MSRA,EPHX1,ANPEP,CAT
	CL:16862	Laminin, N-terminal, and Integrin domain superfamily	4	24	1.18	0.44	0.0211	LAMC1,NID2,ITGB1,LAMA4

	CL:25355	RHO GTPases Activate WASPs and WAVEs, and Regulation of actin polymerization or depolymerization	6	73	0.87	0.42	0.0211	CORO1C,WDR1,CAP2,VASP,CFL1,ACTR3
	CL:21372	Mixed, incl. Serine-type endopeptidase activity, and Metalloexopeptidase activity	8	144	0.7	0.39	0.0246	ANXA4,NAALADL1,LOC540321,NPEPPS,DPP3,BREH1,ENSBTAP00000062769,DPEP1
	CL:21523	Aminopeptidase activity, and Peptidase M12A	4	26	1.14	0.42	0.0264	NAALADL1,NPEPPS,BREH1,DPEP1
	CL:3030	Mixed, incl. Viral nucleoprotein, and ROK, N-terminal	3	10	1.43	0.42	0.0283	HNRNPK,HNRNPA3,HNRNPR
	CL:21521	Mixed, incl. Aminopeptidase activity, and Cystatin domain	5	53	0.93	0.37	0.0353	NAALADL1,NPEPPS,DPP3,BREH1,DPEP1
	CL:9831	Citrate cycle (TCA cycle), and Pyruvate metabolism	5	53	0.93	0.37	0.0353	ACO2,IDH1,DLD,MDH1,ACO1
	CL:9832	Tricarboxylic acid cycle, and Aspartate metabolic process	4	32	1.05	0.35	0.0487	ACO2,IDH1,MDH1,ACO1
	CL:14313	F-actin-capping protein subunit alpha/beta, and Dynactin complex	3	13	1.32	0.35	0.0498	CAPZA1,CAPZB,CAPZA2
Multifocal Animals Versus Diffuse Animals	CL:16669	Mixed, incl. Extracellular matrix organization, and ECM-receptor interaction	19	174	0.9	1.36	5.70e-09	NID1,COL6A1,LAMC1,COL14A1,COL6A3,COL6A2,COL11A1, NID2,FLNA,COL1A2,ITGA1,COL4A1,VCL,ITGB2,TNS1, COL15A1,VCAN,RSU1,FBLN1
	CL:9706	Carbon metabolism, and Pyruvate metabolism	15	123	0.94	1.24	1.80e-08	PGK1,TKT,IDH3A,MDH2,TALDO1,ENO1,PGAM2,TPI1,IDH1, FH,H6PD,SDHB,MDH1,MPST,GPI
	CL:16672	Collagen formation, and Microfibril	11	72	1.04	1.08	9.37e-07	NID1,COL6A1,COL14A1,COL6A3,COL6A2,COL11A1,COL1A2, COL4A1,COL15A1,VCAN,FBLN1
	CL:3017	RNA recognition motif domain, and K Homology domain, type 1	11	73	1.03	1.08	9.37e-07	SYNCRIP,NONO,SFPQ,HNRNPK,HNRNPA3,SRSF7,PCBP1, FUBP1,SRSF1,HNRNPD,HNRNPR
	CL:3020	RNA recognition motif domain, and DZF domain	10	55	1.12	1.11	9.37e-07	SYNCRIP,NONO,SFPQ,HNRNPK,HNRNPA3,SRSF7,PCBP1, SRSF1,HNRNPD,HNRNPR
	CL:9714	Glycolysis, and Transketolase or transaldolase activity	7	23	1.34	1.08	6.22e-06	PGK1,TKT,TALDO1,ENO1,PGAM2,TPI1,GPI
	CL:16677	Collagen chain trimerization, and Complex of collagen trimers	8	37	1.19	1.03	6.20e-07	COL6A1,COL14A1,COL6A3,COL6A2,COL11A1,COL1A2, COL4A1,COL15A1
	CL:3026	mRNA Processing, and Viral RNA genome replication	7	28	1.25	0.97	1.60e-05	HNRNPK,HNRNPA3,SRSF7,PCBP1,SRSF1,HNRNPD,HNRNPR
	CL:9716	Glycolysis, and Transketolase or transaldolase activity	6	16	1.43	1.0	1.88e-05	PGK1,TKT,TALDO1,ENO1,TPI1,GPI
	CL:3021	Mixed, incl. mRNA Processing, and DZF domain	8	47	1.09	0.9	2.03e-05	SYNCRIP,HNRNPK,HNRNPA3,SRSF7,PCBP1,SRSF1, HNRNPD,HNRNPR

	CL:9832	Tricarboxylic acid cycle, and Aspartate metabolic process	7	32	1.2	0.91	2.83e-05	IDH3A,MDH2,IDH1,FH,SDHB,MDH1,MPST
	CL:10453	Amino sugar and nucleotide sugar metabolism, and Starch and sucrose metabolism	8	57	1.0	0.78	6.36e-05	PYGB,GMPPB,GFPT1,PGM1,PGM5,PYGL,GMPPA,UGP2
	CL:9709	Pentose phosphate pathway, and Glycolytic process	8	57	1.0	0.78	6.36e-05	PGK1,TKT,TALDO1,ENO1,PGAM2,TPI1,H6PD,GPI
	CL:16724	Banded collagen fibril, and Activation of protein kinase A activity	5	13	1.44	0.83	0.00014	COL6A1,COL6A3,COL6A2,COL11A1,COL1A2
	CL:20976	Fibrinolysis, and Cystatin-like domain	5	13	1.44	0.83	0.00014	HRG,PLG,F2,ITIH2,FGB
	CL:35224	Mixed, incl. P-type trefoil, chordata, and Lung goblet cell differentiation	5	15	1.38	0.78	0.0011	FCGBP,CLCA1,AGR2,TFF2,REG4
	CL:9735	NADH regeneration, and Peptidyl-cysteine S-trans-nitrosylation	4	6	1.68	0.8	0.00029	PGK1,ENO1,TPI1,GPI
	CL:20964	Complement and coagulation cascades, and Serpin superfamily, domain 2	10	115	0.8	0.65	0.00018	HRG,PLG,F2,CFB,CRP,SERPIND1,ITIH2,LOC506828,AMBP, FGB
	CL:20972	Mixed, incl. Fibrinolysis, and Serine protease inhibitor	6	30	1.16	0.72	0.00023	HRG,PLG,F2,CRP,ITIH2,FGB
	CL:16726	Fibrillar collagen, C-terminal, and Collagen chain trimerization	4	7	1.61	0.76	0.00041	COL6A1,COL6A3,COL6A2,COL1A2
	CL:20966	Complement and coagulation cascades, and Serpin superfamily, domain 2	8	69	0.92	0.68	0.00035	HRG,PLG,F2,CRP,SERPIND1,ITIH2,LOC506828,FGB
	CL:3027	Mixed, incl. Zinc finger, CHHC-type, and Heterogeneous nuclear ribonucleoprotein A1/A2, C-terminal	5	17	1.33	0.74	0.00032	HNRNPK,HNRNPA3,PCBP1,HNRNPD,HNRNPR
	CL:25355	RHO GTPases Activate WASPs and WAVEs, and Regulation of actin polymerization or depolymerization	8	73	0.9	0.64	0.00025	ARPC4,SCIN,GSN,CORO1B,E1BHJ0_BOVIN,ACTR3,ACTR2, TPM4
	CL:9953	Fatty acid beta-oxidation, and Valine, leucine and isoleucine degradation	8	79	0.86	0.6	0.0031	HADH,ACAA1,ALDH9A1,ACADS,OXCT1,ACLY,HADHA, ENSBTAP00000071610
	CL:16857	Mixed, incl. ECM-receptor interaction, and Cell-extracellular matrix interactions	8	80	0.86	0.59	0.0033	LAMC1,NID2,FLNA,ITGA1,VCL,ITGB2,TNS1,RSU1
	CL:20962	Mixed, incl. Complement and coagulation cascades, and Lipoprotein particle	11	164	0.68	0.55	0.0034	HRG,PLG,F2,CFB,LRP1,CRP,SERPIND1,ITIH2,LOC506828, AMBP,FGB
	CL:20965	Complement and coagulation cascades, and Serpin superfamily, domain 2	9	106	0.79	0.58	0.0034	HRG,PLG,F2,CFB,CRP,SERPIND1,ITIH2,LOC506828,FGB
	CL:3030	Mixed, incl. Viral nucleoprotein, and ROK, N-terminal	4	10	1.46	0.66	0.00100	HNRNPK,HNRNPA3,HNRNPD,HNRNPR

	CL:20968	Mixed, incl. Hemostasis, and Serine protease inhibitor	7	60	0.92	0.59	0.0038	HRG,PLG,F2,CRP,SERPIND1,ITIH2,FGB
	CL:9951	Mixed, incl. Fatty acid metabolism, and Valine, leucine and isoleucine degradation	9	110	0.77	0.56	0.0040	HADH,VAT1,ACAA1,ALDH9A1,ACADS,OXCT1,ACLY,HADHA, ENSBTAP00000071610
	CL:26438	COPI-coated vesicle membrane, and COPI-coated vesicle budding	5	24	1.18	0.62	0.0010	COPA,ARF5,COPG1,ARF4,COPB2
	CL:469	Cytoplasmic ribosomal proteins, and Polysomal ribosome	7	61	0.92	0.58	0.00068	RPS17,RPL14,RPL11,RPS16,RPS7,RPL35,RPL5
	CL:10170	Mixed, incl. Alpha-amino acid metabolic process, and One carbon pool by folate	10	142	0.7	0.53	0.0045	ADSL,OTC,SQOR,ALDH18A1,AHCY,ATIC,TST,EIF5A2, SELENBP1,ENSBTAP00000072240
	CL:9954	Fatty acid beta-oxidation, and Valine, leucine and isoleucine degradation	7	67	0.88	0.54	0.0061	HADH,ACAA1,ALDH9A1,ACADS,OXCT1,HADHA, ENSBTAP00000071610
	CL:9956	Fatty acid beta-oxidation, and Ketone body metabolism	6	45	0.98	0.55	0.0061	HADH,ACAA1,ACADS,OXCT1,HADHA,ENSBTAP00000071610
	CL:2408	Chaperone tailless complex polypeptide 1 (TCP-1)	4	13	1.34	0.58	0.020	TCP1,CCT7,CCT6B,CCT6A
	CL:2260	Unfolded protein binding, and Protein folding	8	95	0.78	0.51	0.0010	TCP1,HSP90AA1,CCT7,CCT6B,HSPA8,HSPA2,HSPE1,CCT6A
	CL:25349	Mixed, incl. Regulation of actin polymerization or depolymerization, and Arp2/3 complex binding	9	124	0.72	0.49	0.00095	LCP1,ARPC4,SCIN,GSN,CORO1B,E1BHJ0_BOVIN, ACTR3,ACTR2,TPM4
	CL:10454	Nucleotide-sugar biosynthetic process, and Galactose metabolic process	5	31	1.06	0.52	0.0097	GMPPB,GFPT1,PGM5,GMPPA,UGP2
	CL:426	Cytosolic ribosome	11	194	0.61	0.45	0.00092	RPS17,RPL14,LOC504858,E1B8K9_BOVIN, RPL11,E1BK63_BOVIN,E1BE42_BOVIN,RPS16,RPS7,RPL35, RPL5
	CL:25455	Sequestering of actin monomers	3	5	1.63	0.54	0.0101	SCIN,GSN,E1BHJ0_BOVIN
	CL:37695	MHC class I protein complex assembly, and Beta-2-Microglobulin	3	5	1.63	0.54	0.0101	CALR,TAPBP,CANX
	CL:472	Cytoplasmic ribosomal proteins, and Cytoplasmic side of rough endoplasmic reticulum membrane	6	53	0.91	0.49	0.0112	RPS17,RPL14,RPL11,RPS7,RPL35,RPL5
	CL:26440	COPI-coated vesicle membrane, and COPI coating of Golgi vesicle	4	17	1.23	0.51	0.0119	COPA,COPG1,ARF4,COPB2
	CL:16804	Mixed, incl. Anaphylatoxin homologous domain, and Laminin EGF domain	3	6	1.56	0.5	0.0137	NID1,VCAN,FBLN1

	CL:35226	Mixed, incl. Lung goblet cell differentiation, and Proteinase inhibitor I1, Kazal-type, metazoa	3	6	1.56	0.5	0.0137	FCGBP,CLCA1,AGR2
	CL:460	GTP hydrolysis and joining of the 60S ribosomal subunit, and Cytosolic ribosome	8	108	0.73	0.44	0.0137	RPS17,RPL14,RPL11,E1BK63_BOVIN,RPS16,RPS7,RPL35,RPL5
	CL:2252	Protein folding, and Cellular response to unfolded protein	9	140	0.66	0.43	0.0145	TCP1,HSP90AA1,CCT7,CCT6B,HSPA8,HSPA2,TXNDC5,HSPE1, CCT6A
	CL:10171	Alpha-amino acid metabolic process, and One carbon pool by folate	8	111	0.71	0.43	0.0154	ADSL,SQOR,ALDH18A1,AHCY,ATIC,TST,SELENBP1, ENSBTAP00000072240
	CL:14309	COPI-independent Golgi-to-ER retrograde traffic, and Golgi to secretory granule transport	4	19	1.18	0.47	0.0159	CAPZA1,CAPZA2,DCTN2,ACTBL2
	CL:9834	TCA cycle, and Glyoxylate cycle	4	19	1.18	0.47	0.0159	IDH3A,IDH1,FH,SDHB
	CL:26446	COPI vesicle coat	3	7	1.49	0.47	0.0176	COPA,COPG1,COPB2
	CL:37354	Immunoglobulin complex, circulating, and Immunoglobulin V-Type	5	40	0.95	0.42	0.0221	G5E513_BOVIN,JCHAIN,LOC100300716, ENSBTAP00000058812,ENSBTAP00000064749
	CL:2410	Chaperonin TCP-1, conserved site	3	8	1.43	0.44	0.0228	TCP1,CCT7,CCT6A
	CL:440	Cytosolic ribosome	9	152	0.63	0.39	0.0229	RPS17,RPL14,RPL11,E1BK63_BOVIN,E1BE42_BOVIN,RPS16, RPS7,RPL35,RPL5
	CL:10455	Nucleotide-sugar biosynthetic process, and Galactose metabolic process	4	22	1.12	0.43	0.0232	GMPPB,PGM5,GMPPA,UGP2
	CL:25357	Arp2/3 protein complex, and Negative regulation of actin nucleation	4	23	1.1	0.41	0.0263	ARPC4,CORO1B,ACTR3,ACTR2
	CL:16967	Mixed, incl. Cell-extracellular matrix interactions, and Alpha-catenin/vinculin-like superfamily	4	25	1.06	0.39	0.0322	FLNA,VCL,TNS1,RSU1
	CL:9876	Aspartate metabolic process, and Aminotransferase ALAT1/2-like	3	10	1.33	0.4	0.0335	MDH2,MDH1,MPST
	CL:475	Cytoplasmic ribosomal proteins, and Polysomal ribosome	5	48	0.87	0.36	0.0385	RPS17,RPL14,RPL11,RPS7,RPL35
	CL:19615	Mixed, incl. ESCRT complex, and S100/CaBP-9k-type, calcium binding, subdomain	7	103	0.69	0.34	0.0392	KRT20,CHMP4B,STOM,AHNAK,ANXA3,CD63,ANXA8L1
	CL:22445	Myosin II filament, and Smooth Muscle Contraction	3	11	1.29	0.38	0.0393	MYH9,ACTA2,MYH10
	CL:25365	Arp2/3 protein complex	3	11	1.29	0.38	0.0393	ARPC4,ACTR3,ACTR2

	CL:479	Cytoplasmic ribosomal proteins, and Ribosomal protein S30	4	28	1.01	0.36	0.0423	RPS17,RPL14,RPL11,RPL35
	CL:14250	Cytoplasmic dynein complex, and Dynactin complex	5	50	0.86	0.35	0.0424	CAPZA1,CAPZA2,DCTN2,ACTBL2,DYNC1I2
	CL:2666	U2 snRNP, and Small nuclear ribonucleoprotein F	4	29	1.0	0.35	0.0455	SNRPN,SF3B3,SNRPD1-3,SNRPD3
	CL:9958	Fatty acid beta-oxidation, and CoA-transferase family III	4	29	1.0	0.35	0.0455	ACAA1,ACADS,HADHA,ENSBTAP00000071610

Supplementary Table 3. Local protein-protein interaction networks identified by STRING analysis from differentially expressed proteins (DEPs) in the ileocecal valve for each experimental comparison.

Networks were generated using STRING v12.0 with a minimum interaction confidence score of 0.70. Only clusters with statistically significant enrichment (FDR < 0.05) are shown. B-gene count: Background gene count; St: strength; S: signal; FDR: False Discovery Rate.

Tissue / Fraction Source	Supporting Peptide Sequence	Sequence Variation / Variant Type	PEAKS Score (-10lgP)
FOCAL-ZN	R.LSTIIDSDMIL(sub M)VLDSGTVKEYSPPHVLLQ.N	Leu → Met Substitution (sub M)	24.87
FOCAL	R.AP(sub S)VLFFNSNPIGR.I	Pro → Ser Substitution (sub S)	48.62
	R.AP(sub S)L(sub V)LFFNSNPIGR.I	Double Substitution (sub S / sub V)	39.03
	R.LSTIIDSDMIL(sub M)VLDSGTVKEYSPPHVLLQ.N	Leu → Met Substitution (sub M)	29.73
	R.LSTIIDSDMIMVLDSGV(sub T)VKEYSPPHVLLQ.N	Thr-site Variant Substitution (sub T)	20.53
	R.ALLGELPR(sub P).S	Arg → Pro Substitution (sub P)	22.36
	K.SGVDIFSPY(sub F)EKR(sub G).N	Double Substitution (sub F / sub G)	16.78
	Global Profile Feature	Ser->Pro Point Mutation	48.62*
	Global Profile Feature	Val->Leu Point Mutation	39.03*
	Global Profile Feature	Met->Leu Point Mutation	29.73*
FOCAL-NEG	R.LSTIIDSDMIL(sub M)VLDSGTVKEYSPPHVLLQ.N	Leu → Met Substitution (sub M)	15.09
MULTIFOCAL-WCS	G.MFTFLY(ins)EEGTR.V	Structural Sequence Insertion (ins)	17.41
	R.LM(sub S)TIIDSDMIMVLDSGTVKEYSPPHVLLQ.N	Met → Ser Substitution (sub S)	15.31
MULTIFOCAL	R.ALLGELPR(sub P).S	Arg → Pro Substitution (sub P)	15.77
DIFFUSE	*No mutated peptides survived filtering thresholds*	Undetected / Wild-type Sequence	—
NO-LESIONS	*No mutated peptides survived filtering thresholds*	Undetected / Wild-type Sequence	—

Supplementary Table 4. High-confidence peptide sequence variants identified in bovine Multidrug Resistance-Associated Protein 4 (ABCC4; UniProt accession: tr|A0A3Q1LXZ2) across tissue fractions associated with different lesion profiles of bovine paratuberculosis (PTB), using mass spectrometry-based homology mapping. The table reports supporting peptide sequences, sequence variation types, and PEAKS confidence scores (−10lgP). Amino acid substitutions are indicated by the corresponding residue change and variant position, whereas “ins” denotes an amino acid insertion. An asterisk (*) indicates a high PEAKS Score. FOCAL-ZN represents animals with focal lesions positive only by Ziehl–Neelsen staining;

FOCAL, animals with focal lesions; FOCAL-NEG, animals with focal lesions negative by all diagnostic methods; MULTIFOCAL-WCS, animals with multifocal lesions without clinical signs; MULTIFOCAL, animals with multifocal lesions, including both diagnostic-positive and diagnostic-negative animals; DIFFUSE, animals with diffuse lesions; NO-LESIONS, animals without lesions associated with PTB. The identified peptide variants included single- and double-amino-acid substitutions and a sequence insertion. FOCAL tissue fractions displayed the greatest number of distinct peptide variants and the highest PEAKS Scores, including the recurrent LSTIIDSDMIL… peptide variant. The Leu→Met substitution within this peptide was also detected in FOCAL-ZN and FOCAL-NEG fractions. MULTIFOCAL-WCS fractions exhibited two distinct sequence variants, comprising an insertion and a Met→Ser substitution, whereas the MULTIFOCAL category showed an Arg→Pro substitution. No mutated peptides passed the applied filtering thresholds in DIFFUSE or NO-LESIONS fractions. These findings indicate lesion-associated heterogeneity in the detected ABCC4 peptide sequence profiles, with distinct variant patterns across focal and multifocal lesion categories.

Supplementary Methods. Long version of the methods used in the Data-Independent Acquisition (DIA) sequential window acquisition of all theoretical fragment ion spectra (SWATH-MS) quantitative proteomics to identify differentially expressed proteins across groups (animals with multifocal lesions *versus* no-lesions control group, animals with multifocal lesions *versus* animals with diffuse multibacillary lesions, and animals with diffuse multibacillary lesions *versus* no-lesions control group).

Proteomic assay performance

Samples of serum and ICV were analysed by Data-Independent Acquisition (DIA) with quantitative Sequential Window Acquisition of all Theoretical Fragment Ion Spectra (SWATH)-MS proteomics to identify differential expressed proteins (DEP) between groups as previously described (Del Pilar Chantada et al., 2019; Alvarez et al., 2020).

First of all, 30µL of serum and ICV extracts were depleted of high-abundant serum proteins using dithiothreitol (DTT) following the protocol described by Warder et al. (2009) and Fernández et al. (2011), This step enriched the low-abundance protein fraction, enhancing the resolution of low expressed proteins. The samples were prepared to have an equal amount of protein and were analysed on a 10 % SDS-PAGE gel. Protein bands were detected using Sypro-Ruby fluorescent staining (Lonza, Basel, Switzerland), manually excised, and processed for in-gel tryptic digestion, as previously described (Shevchenko et al., 1996).

Briefly, for trypsin digestion, protein bands were first washed with a solution 50% (v/v) of 50 mM ammonium bicarbonate (Sigma-Aldrich, Saint Louis, USA) / methanol (HPLC grade, Scharlau, Barcelona, Spain) and dehydrated in acetonitrile (ACN) (HPLC grade, Scharlau, Barcelona, Spain). These bands were reduced in 10 mM dithiothreitol (Sigma-Aldrich, Saint Louis, USA) in 50 mM ammonium bicarbonate at 56◦C for 30 min, followed by an alkylation step using 55 mM iodoacetamide (Sigma-Aldrich, Saint Louis, MO) in 50 mM ammonium bicarbonate for 20 min at room temperature (RT) in darkness. Protein bands were rinsed with 50% (v/v) of 50 mM ammonium bicarbonate/methanol and dehydrated with acetonitrile. Finally, tryptic digestion was carried out by adding modified porcine trypsin (Promega, Madison, WI, USA) at a final concentration of 20 ng/µL in 20 mM ammonium bicarbonate and incubating for 16 h at 37 ◦C. Tryptic peptides were extracted generated through three consecutive

20-minute incubations in 40 µL of 60% acetonitrile containing 0.5% formic acid. The resulting extracts were pooled, vacuum-dried, and stored at -20°C for subsequent analysis.

For Data-Dependent Acquisition (DDA) , digested peptides (> 4 µg of each sample) from all samples were analyzed with a reverse phase liquid chromatography coupled to Triple-TOF mass spectrometry (nano LC-ESI-MS/MS) analysis using a nano liquid chromatography system (Eksigent Technologies nanoLC 400, SCIEX Foster City, CA, USA) coupled to a high-speed Triple TOF 6600 mass spectrometer (SCIEX, Foster City, CA, USA) as described previously (Alvarez et al., 2020).

Digested peptides separation was performed on a silica-based reversed phase column C18 150 × 0.30 mm, with a 3 mm particle size and 120 Å pore size (Eksigent, SCIEX, Foster City, CA, USA) with a trap column YMC-TRIART C18 (YMC Technologies, Teknokroma). Peptides were fractionated at a flow rate of 5 µL/min in a 90 min gradient with increasing concentrations of ACN (2% to 90%). Triple-TOF 6600 system was operated with the following settings: ion spray voltage floating (ISVF) 5500 V, curtain gas (CUR) 25, collision energy (CE), 10 and, ion source gas 1 (GS1) 25. The instrument was operated with Analyst TF 1.7.1 software (SCIEX, Foster City, CA, USA). MS/MS fragmentation was performed in 350−1400 m/z range considering a charge state of 2−5. Dynamic exclusion was set to 15 s. The mass spectrometry data obtained were processed using ProteinPilot TM 5.0.1 software (SCIEX, Foster City, CA, USA). Data were searched using the Bos taurus protein database (UniProt knowledgebase) in order to identify cysteine alkylation as a fixed modification and methionine oxidation as a variable modification and determine relative abundance at a >95% confidence interval. A non-lineal false discovery rate (FDR) was applied for peptide identification. only peptides with FDR < 1% cutoff were considered.

For quantitative analysis, a SWATH-MS analysis was performed. First of all, a mass spectrometry (MS/MS) spectral library is generated. Equal volumes from the original samples were combined to create pooled vials for each group, ensuring the representation of all peptides and proteins across all samples. These pools of peptide solutions per condition were analysed using a shotgun DDA approach by micro-LC-MS/MS (SCIEX, Foster City, CA, USA), as described above and previously described (Alvarez et al., 2020). The spectral library for SWATH peak extraction was

constructed from the MS2 spectra (MS/MS spectra) of the identified peptides using an add-on for PeakView Software (version 2.2, SCIEX): MS/MSALL with SWATH Acquisition MicroApp (version 2.0, SCIEX). Only peptides with a confidence score >99% were included.

SWATH–MS acquisition was performed on a TripleTOF® 6600 LC-MS/MS system (SCIEX, Foster City, CA, USA). The analysis is carried out in technical triplicate on each sample studied using a DIA method. Each 4-µL sample was analyzed with the LC-MS equipment, applying the aforementioned LC gradient used to build the spectral library, but using the SWATH-MS acquisition method instead described previously (Del Pilar Chantada et al., 2019; Alvarez et al., 2020).

The SWATH-MS method consisted of the cyclic acquisition of 100 TOF MS2 (MS/MS) scans. The Triple-TOF 6600 system was configured with MS/MS fragmentation in the range 400-1500 m/z, operating in high sensitivity mode, with an acquisition time of 50 ms. The cycle included overlapping sequential precursor isolation windows of variable width (1 m/z overlap), covering the range 400-1250 m/z. Each cycle was preceded by a TOF MS1 scan (400-1500 m/z, 50 ms acquisition time). The total cycle time was 6.3 seconds. The widths of the 100 variable windows were optimised based on the ion density data from the DDA runs, using a SWATH variable window calculator (SCIEX, Foster City, CA, USA).

Data analysis for proteomic assay performance

The targeted data extraction of the fragment ion chromatogram traces from the SWATH runs was performed by PeakView (version 2.2) using the SWATH Acquisition MicroApp (version 2.0). This application processed the data using the spectral library created from the shotgun data. Up to ten peptides per protein and seven fragments per peptide were selected, based on signal intensity; any shared and modified peptides were excluded from the processing. Five-minute windows and 30 ppm widths were used to extract the ion chromatograms; SWATH quantization was attempted for all proteins in the ion library that were identified by ProteinPilot with an FDR below 1%. The retention times from the peptides that were selected for each protein were realigned in each run according to the iRT peptides spiked in each sample and eluted along the whole time axis. The extracted ion chromatograms were then generated for each selected fragment ion; the peak areas for the peptides were obtained by summing the

peak areas from the corresponding fragment ions. PeakView computed an FDR and a score for each assigned peptide according to the chromatographic and spectra components; only peptides with an FDR below 1% were used for protein quantization. Protein quantization was calculated by adding the peak areas of the corresponding peptides.

The integrated peak areas (processed. mrkvw files from PeakView) were directly exported to the MarkerView software (Sciex) for relative quantitative analysis. The export will generate three files containing quantitative information about individual ions, the summed intensity of different ions for a particular peptide and the summed intensity of different peptides for a particular protein. MarkerView has been used for analysis of SWATH-MS data reported in other proteomics studies because of its data-independent method of quantization. MarkerView uses processing algorithms that accurately find chromatographic and spectral peaks direct from the raw SWATH data. The software's alignment of the data compensates for small variations in the mass and RT values, ensuring precise comparisons of identical compounds in different samples. To homogenise the data obtained, a most likely ratio (MLR) normalisation was performed (Lambert et al., 2013). Unsupervised multivariate statistical analysis using principal component analysis (PCA) was performed to compare the data across the samples. The average MS peak area of each protein was derived from the replicates of the SWATH-MS of each sample, followed by Student's t-test analysis using the MarkerView software for comparison among the samples based on the averaged area sums of all the transitions derived for each protein. Statistical significance differences between groups were evaluated using the Mann-Whitney U-test or Student's t-test. Proteins were considered as DEPs those with a FDR-corrected p-values <0.05 and a FC > 1.5 fold in- or <0.6.

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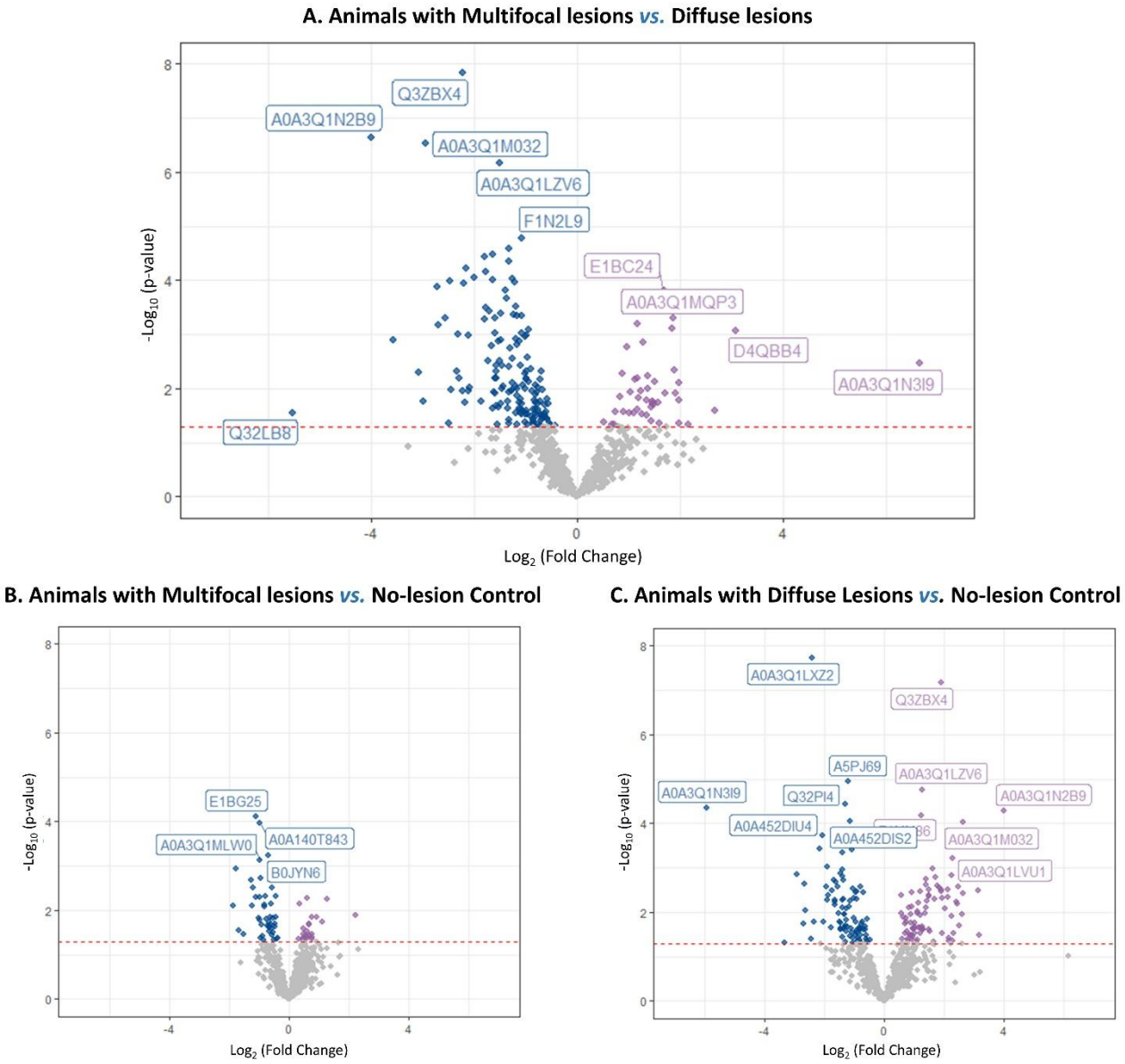
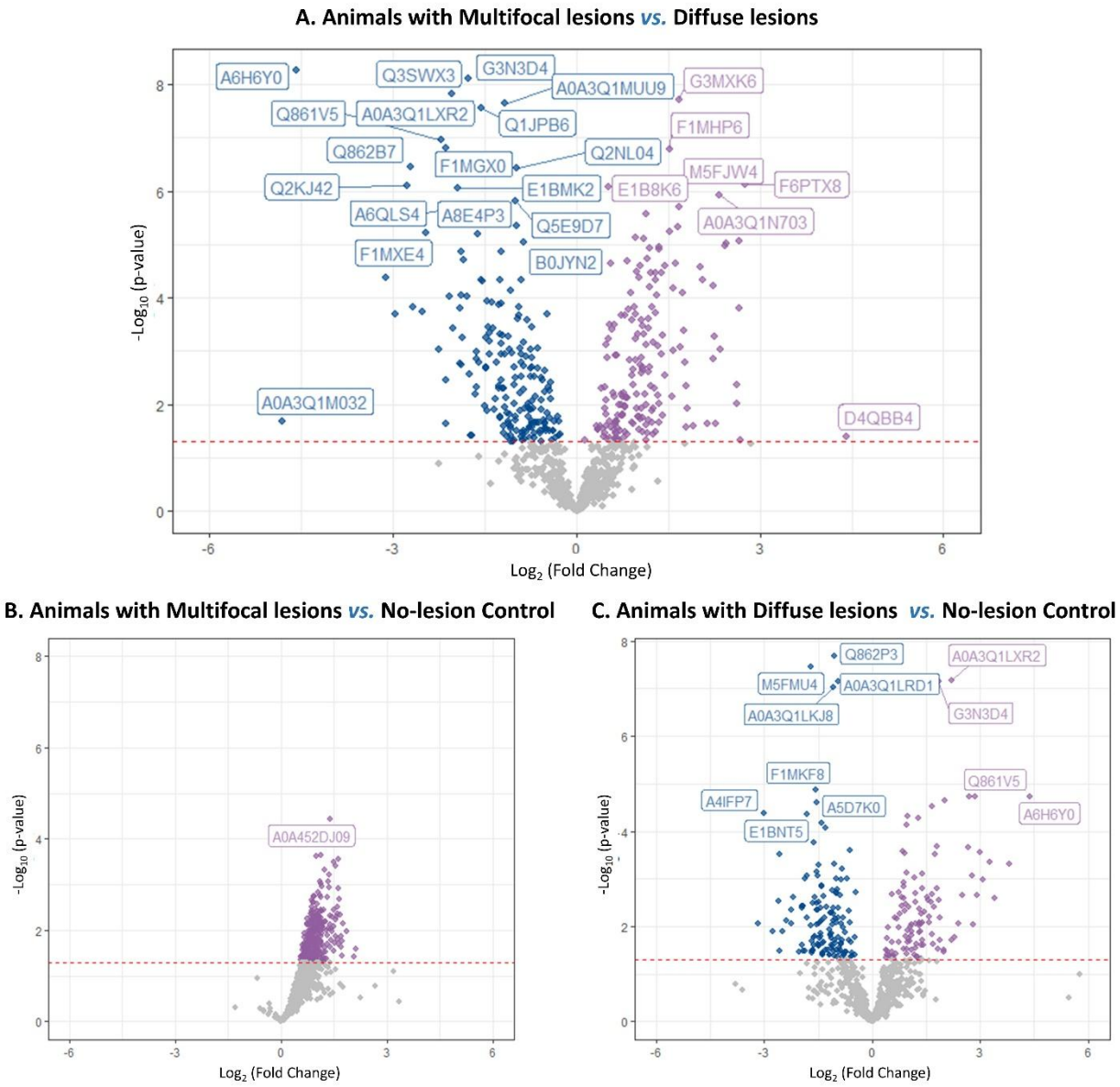
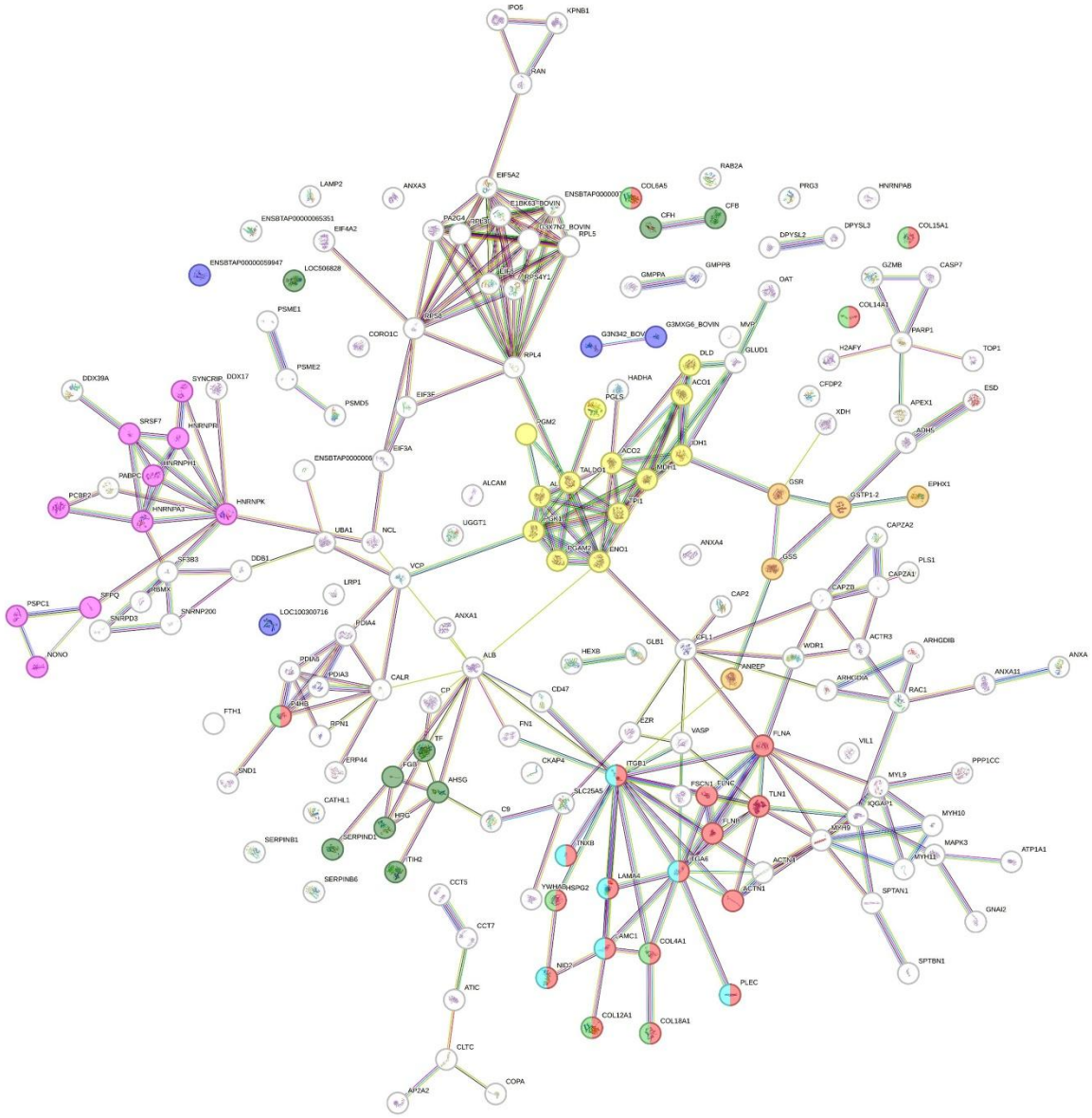


Supplementary Figure 1. Volcano plots showing both differentially expressed proteins (DEPs) and non-DEPs identified by SWATH-MS analysis in serum. (A) Animals with multifocal lesions *versus* (*vs.*) animals with diffuse multibacillary lesions comparison; (B) Animals with multifocal lesions *vs.* no-lesions control animals' comparison, and (C) Animals with diffuse multibacillary lesions *vs.* no-lesions control animals. The x-axis shows $\log_2$ fold change values, while the y-axis represents the $-\log_{10}$ p-values reflecting statistical significance. Significantly upregulated proteins are marked in violet, significantly downregulated in blue, and non-significant changes in grey. Selected DEPs are labelled by their Uniprot accession numbers.

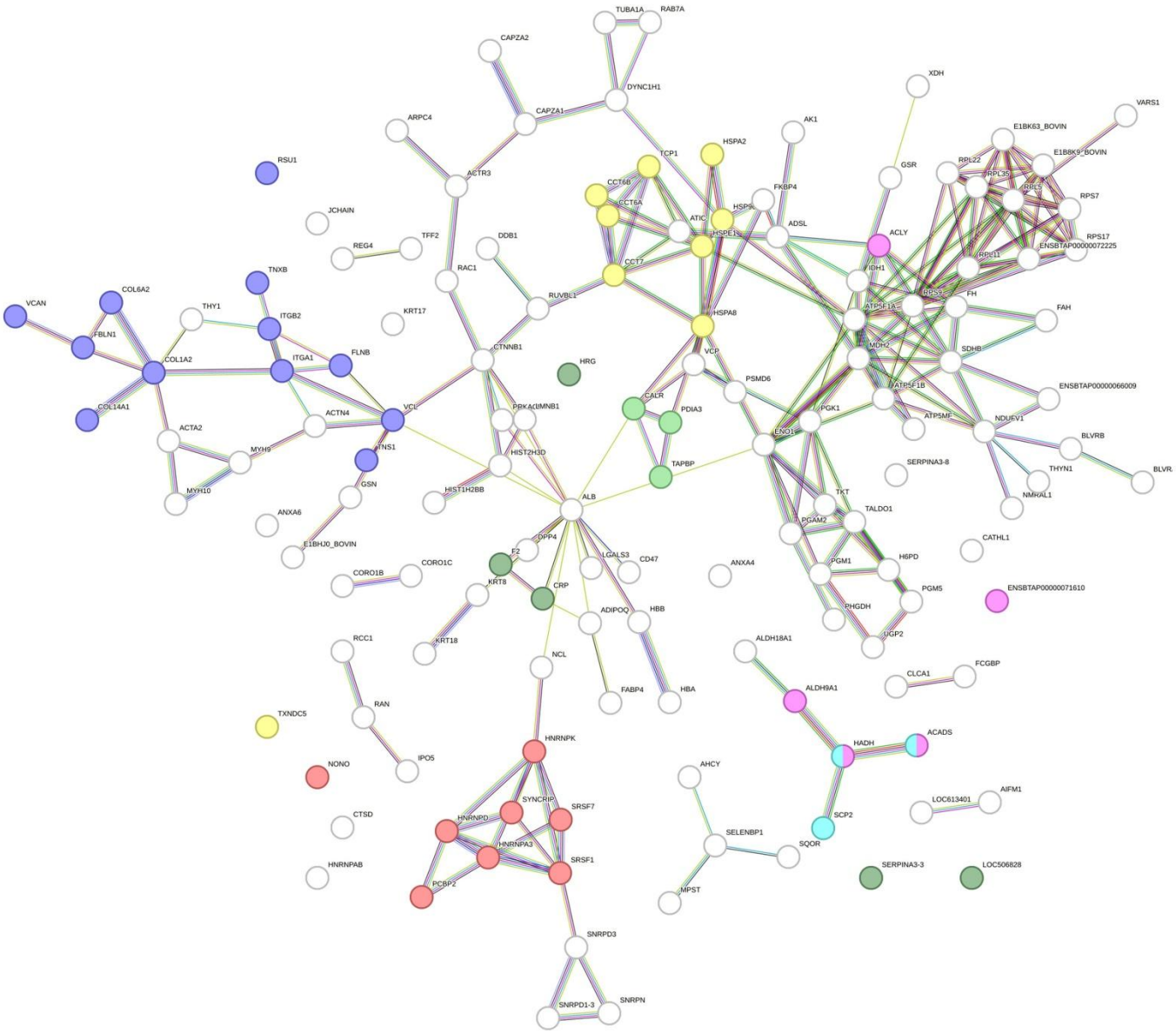


Supplementary Figure 2. Volcano plots showing both differentially expressed proteins (DEPs) and non-DEPs identified by SWATH-MS analysis in ileocecal valve. (A) Animals with multifocal lesions *versus* (*vs.*) Animals with diffuse multibacillary lesions comparison; (B) Animals with multifocal lesions *vs no-lesions* control animals comparison, and (C) Animals with diffuse multibacillary lesions *vs.* no-lesions control animals. The x-axis shows $\log_2$ fold change values, while the y-axis represents the $-\log_{10}$ p-values reflecting statistical significance. Significantly upregulated proteins are marked in violet, significantly downregulated in blue, and non-significant changes in grey. Selected DEPs are labelled by their Uniprot accession numbers.



Supplementary Figure S3. STRING-based network analysis of ileocecal valve proteins from Animals with diffuse multifocal lesions versus no-lesion control animals. Functional network analysis of differentially expressed proteins in ileocecal valve of multifocal phenotype versus no-lesion control animals using STRING functional enrichment analysis. The figure represents merged networks 1-8 with at least six main nodes observed related to (1) extracellular matrix organization, ECM-receptor interaction, Cell-ECM interactions, and Talin (20 bright red proteins: Alpha-actinin-1 (ACTN1), Talin 1 (TLN1), Filamin C (FLNC)); (2) RNA recognition motif domain, DZF domain, mRNA processing and Zinc finger (10 proteins represented in bright pink that includes: Heterogeneous nuclear ribonucleoprotein K ((HNRNPK), Non-POU domain containing octamer binding (NONO) and Serine/arginine-rich-splicing factor 7 (SRSF7));(3) Mixed, Incl. Carbon metabolism, Pyruvate metabolism, Glycolysis, Pentose phosphate and TCA Cycle (13 proteins represented in yellow that includes: Phosphoglycerate kinase (PGK1);(4) Complement and coagulation cascades and Serpin superfamily, domain 2 (9 proteins represented in dark green that includes: HRG, complement factor B (CFB) and Complement factor H (CFH)); (5) Integrin complex, Laminin

(7 blue proteins: Laminin subunit alpha 4 (LAMA4), Integrin subunit alpha 6 (ITGA6) and Plectin (PLEC));(6) Collagen biosynthesis, formation, and microfibril (8 bright green proteins: proteoglycan 2 (HSPG2), Collagen alpha-1(IV) chain (COL4A1), and Protein disulfide-isomerase (P4HB)); (7) Mixed, Incl. Glutathione metabolism, Detoxification of Reactive Oxygen Species and Cell redox homeostasis (4 orange proteins: Glutathione synthetase (GSS)); (8), Immunoglobulin complex, circulating, and Immunoglobulin V Type (5 violet: Ig-like domain-containing protein (G3MXG6)). Only 179 proteins inputs are represented for clarity of the graph. Coloured lines indicate direct associations that are meant to be specific and meaningful, bright blue and pink lines are known interactions from curated databases and experimentally determined, respectively. Dark green, red and dark blue lines are predicted interactions from gene neighbourhood, gene fusions and gene co-occurrence, respectively. Bright green, black and violet lines are interactions derived from textmining, co-expression and protein homology, respectively.



Supplementary Figure S4. STRING-based network analysis of ileocecal valve proteins from Animals with diffuse multibacillary lesions versus no-lesion control animals. Functional network analysis of differentially expressed proteins in the ileocecal valve of diffuse animals versus no-lesion control animals using STRING. The figure represents merged networks 1-7 with at least six main nodes observed related to (1) RNA recognition motif / KH domains and RNA processing (8 proteins represented in bright red that includes: Non-POU domain containing octamer binding (NONO), Synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP) and HNRNPD protein (HNRNPD)); (2) Extracellular matrix organization / ECM-receptor interaction (12 proteins coloured in violet that includes: Tensin 1 (TNS1), Versican core protein (VCAN) and Integrin subunit alpha 1 (ITGA1)); (3) Protein folding, and Cellular response to unfolded protein (9

proteins represented in yellow that includes: T-complex protein 1 subunit eta (CCT7), Heat shock cognate protein (HSPA8) and 10 kDa heat shock protein, mitochondrial (HSPE1));(4) MHC class I protein complex assembly, and Beta-2-Microglobulin (3 proteins coloured in bright green that includes: Protein disulfide-isomerase (PDIA3), and TAP binding protein (TAPBP));(5) Mitochondrial long chain fatty acid beta-oxidation (3 proteins represented in dark green that includes: 4-trimethylaminobutyraldehyde dehydrogenase (ALDH9A1), and Hydroxyacyl-CoA dehydrogenase (HADH); Short-chain-specific acyl-CoA dehydrogenase, mitochondrial (ACADS)); (6) Fatty acid beta-oxidation, and Valine, leucine and isoleucine degradation (5 pink proteins: Non-specific lipid-transfer protein (SCP2), HADH, and ACADS); and (7) Complement and coagulation cascades, and Serpin superfamily, domain 2 (5 blue proteins: Histidine-rich glycoprotein (HRG), and Serpin A3-3 (SERPINA3-3)). Only 146 protein inputs are represented for clarity of the graph. Coloured lines indicate that direct associations are meant to be specific and meaningful; bright blue and pink lines are known interactions from curated databases and experimentally determined, respectively. Dark green, red and dark blue lines are predicted interactions from gene neighbourhood, gene fusions and gene co-occurrence, respectively. Bright green, black and violet lines are interactions derived from text mining, co-expression and protein homology, respectively.