SUPPLEMENTARY TABLE 7.
Signaling pathways in the developing ENS

Gene:	Online ISH resources:	IHC:	Current screen:	Comment/ References:
***Activin A signaling**				Comment: Function in CNS[1]
Inhba* (homodimerize to Activin A)	mesenchyme E11-13	**In the ENS, Fig 5B, 6; S6**	C11vsW11 C15vsW15	
Inha* (heterodimer with INHBA to form Inhibin)	N/D	**In the ENS, Fig 6; S6, 7**	W15vsC15 W15vsS15 W15vsW11	
Acvr1b* (*Alk4*)	ENS E14-15 Fig. 5B		W15vsC15 S15vsC15	
Acvr2a*	ENS E13-15	**In the ENS, Fig 5B, 6; S6, 7**	W15vsC15 W15vsW11 S15vsC15	
***ALK/LTK signaling**				Comment: Function in neural crest[2]
Alk	ENS E15 **S5**		W15vsC15 W15vsS15 >2,5	In bowel wall[3]
Ltk*	ENS E13-E15 **Fig. 5C**		W15vsC15 W15vsS15	
***Aryl-hydrocarbon signaling**				Comment: Function in CNS[4]
Ahr*	General gut E14	**In the ENS, Fig. 5C, 6; S6, 7**	W11vsC11 S15vsC15 S15vsS11	
Arnt2*	ENS E13-15 **S5**		W15vsC15 S15vsC15	
BMP signaling				Well-studied in ENS[5]
Bmp1*	General gut E13-15, S4		C15vsW15	
Bmp2	mesenchyme E14		C15vsW15	In bowel[6]
Bmp4	Serosa, mesenchyme E14		C11vsW11 C15svW15	In bowel[6]
Bmp5*	mesenchyme E11-15, **S5**		C11vsW11 C15svW15	In adult colon[7]
Bmp6*	mucosa E15 **S5**		C15vsW15	
Bmp7*[ENS]	ENS and mucosa E15 **Fig. 5B**		S11vsC11 S15vsC15 >2.3	In chick mesenchyme[8] Comment: Function in CNS[9]
Gdf6* (***Bmp13***)	General gut, close to ENS E11-15 **S5**		C11vsW11 C15vsW15	

Gdf10* (***Bmp3b***)	ENS and serosa E13-15	**In the ENS Fig. 5B, 6; S6, 7**	W11vsC11 C15vsW15	Comment: Function in other system[10]
Acvr1a* (***Alk2***)	ENS E15	**In the ENS, Fig. 5B, 6; S6, 7**	S11vsC11 S15vsS11	
Bmpr1b (***Alk6***)	N/D		W15vsC15 W15vsW11 W15vsS15	In ENS and mesenchyme (RT-PCR)[6]
Acvr2a*	ENS and mucosa E13-15	**In the ENS, Fig. 5B, 6; S6, 7**	W15vsC15 S15vsC15	
Bmpr2	General gut E11-15		W15vsW11	In ENS (RT-PCR)[6]
***Chemokine signaling**				Comment: Function in CNS[11-13]
Cxcl12*	serosa and mesenchyme E11-E15	**serosa and mucosa Fig. 5D, 6; S6, 7**	C15vsW15	
Cxcr4*	ENS E11-E15	**In the ENS, Fig. 5D, 6; S6, 7**	W15vsC15 W15vsW11 W15vsS15	$Cxcr4^{-/-}$ mutant display ENS migration defect[14] Not detected in developing ENS before, but in adult ENS ganglia[15]
***CCN family matricellular modulators**				Comment: Function in other systems[16]
Ctgf* (*Ccn2*)	ENS and mucosa E13-E15	**In the ENS, Fig. 5B, 6; S6, 7**	S15vsC15 S15vsS11 S15vsW15	
Ngfr (p75)	ENS E11-E15		W11vsC11 W15vsC15	In the ENS[17]
Itga2	N/D		S15vsC15 S15vsS11 S15vsW15 >1,7-2,7	
Endothelin signaling				Well-studied in ENS[18]
Edn1*	mucosa E14 **S5**		C11vsW11	
Edn3	mesenchyme E14		C11vsW11 C15vsW15	In gut mesenchyme[19] HSCR locus[20]
Ednrb	ENS and mesenchyme E13-15		W11vsC11 W15vsC15	In the ENS[21] HSCR locus[20]
***Eph/ephrin signaling**				Comment: Function in other systems[22]
Efna1*	mesenchyme E11-15, **S4**		C15vsW15	
Efna4*	mesenchyme mucosa E11-15 **S4**		W11vsW15	

Efna5*	mesenchyme, ENS E13-15 **Fig. 5B**		W15vsW11	
Efnb1*	mesenchyme E11-E14, **S5**		C15vsW15	
Efnb2*	mesenchyme E11-15, **S5**		C11vsW11 C15vsS15	
Efnb3*	ENS E13-15 **Fig. 5B**		W15vsC15 W15vsW11 W15vsS15	
Epha5*	ENS E14-E15 **Fig. 5B**		W15vsC15 W15vsW11 W15vsS15	
Epha6*	N/D		W15vsC15 W15vsW11 W15vsS15 >2.2-3.6	
Ephb2*	ENS E14-15 **Fig. 5B**		S11vsC11	
***FGF signaling**				Comment: Function in other system[23, 24]
Fgf1*	General gut E11-15	**In the ENS, Fig. 5B, 6; S6, 7**	W15vsW11	
Fgf7*	N/D		S15vsW15 W11vsC11 S11vsC11 >1,5	
Fgf9	serosa and mesenchyme E11-14		C11vsW11 C15vsW15	In gut mesenchyme[25]
Fgf10	Stomach and hindgut mesenchyme E11-E15		C11vsW11 C15vsW15	In gut mesenchyme[26]
Fgf13	ENS E14		W11vsC11 W15vsC15	In the ENS[27, 28]
Ffgr1*	serosa mesenchyme E11-15	**In the ENS, Fig. 5B, 6; S6, 7**	C15vsW15	
Fgfr2	bowel wall E14 **S5**		C11vsW15 C15vsW15	
***FLRT/UNC-5D signaling**				Comment: Function in CNS[29, 30]
Flrt1	Mesentery, ENS? E14 **S5**		W15vsC15 S15vsS11 S15vsC15 >1,26	ENS transcriptome[31]
Flrt2*	mesenchyme and ENS E14 **Fig. 5B**		W11vsW15 W15vsS15 >1,4	
Flrt3*	mesenchyme E14, **S5**		C11vsW11 C15vsW15	
Lphn1* **(bind UNC-5D and FLRT)**	N/D		W15vsC15 W15vsS15 W15vsW11	

			>1,49	
Unc5d*	Few ENS cells E13-15 **Fig. 5B**		W15vsC15 W15vsS15 W15vsW11	
GDNF/Nrtn signaling				Well-studied in ENS[18]
Gdnf	mesenchyme E11-15		C11vsW11 C15vsW15	In gut mesenchyme HSCR locus[32]
Nrtn	mesenchyme E14		N/D	In the ENS[33, 34]
Ret	ENS E11-15		W11vsC11 W15vsC15	In the ENS HSCR locus[35]
Gfra1	ENS and mesenchyme E11-15		W11vsC11 W15vsC15	In the ENS[36]
Gfra2	ENS and mesenchyme E13-15		W11vsC11 W15vsC15	In the ENS[37]
Hedgehog signaling				Well-studied in ENS[38]
Ihh	mucosa E14		N/D	In mucosa[39]
Shh	mucosa E11-15		N/D	In mucosa[39]
Dhh	N/D		S15vsC15	In Schwann-cell derived ENS[40]
Ptch1	ENS and muscle E11-14		W11vsW15	In the ENS[39]
Smo	general gut E13		W11vsW15	In the ENS[41]
Gas1	serosa, muscle and ENS E15		C15vsW15	In the ENS[41]
***IGF/Insulin signaling**				Comment: Function in other systems[42]
Igf1*	mesenchyme E11-15	**Mesenchyme and ENS. Fig. 5B, 6; S6, 7**	C11vsW11 C15vsW15	In adult ENS[43]
Igf2*	mucosa and serosa E11-15 **S5**		C11vsW11 C15vsW15	
Igf1r*	mesenchyme E11-15	**In the ENS, Fig. 5B, 6; S7**	W11vsC11 W15vsC15	In adult ENS[43]
Insr*	Few ENS cells E13-E15, **S5**		W15vsC15	
***Midkine signaling**				Comment: Function in other systems[44]
Ptn	Mesenchyme E14		C11vsW11 C15vsW15	In mesenchyme[45]
Mdk*	Mesenchyme ENS? E14	**In the ENS, Fig. 5B, 6; S6, 7**	C11vsW11 C15vsW15 W11vsW15	
Ptprz1	ENS E13-15		W11vsC11 W15vsC15	ENS

	S5		W15vsW11 >3-30	transcriptome[31]
Itga4	ENS E11-14 **S5**		W11vsC11 W11vsW15	In human iPS-derived ENSCs[31, 46]
Itga6	ENS and mucosa E14 **Fig. 5B**		W11vsC11 W15vsC15 W11vsW15	ENS transcriptome[31]
***Cspg5* (*Ngc*)**	ENS E14?		W11vsC11 W15vsC15 W15vsW11	In the ENS[47]
Netrin signaling				Studied in ENS[18]
Ntn1	mesenchyme E13-15			In the ENS[48]
Ntn3	mesenchyme E13-15			In the ENS[48]
Ntn4*	Few ENS cells E15, **S5**		W15vsC15 S15vsC15	
Ntng1*	ENS E13-15 **Fig. 5C**		W15vsC15 W15vsS15 W15vsW11	
Lrrc4c*	N/D		W11vsC11 W15vsC15 W15vsW11 >4-11	Comment: Function in CNS[49]
Unc5d*	Few ENS cells E13-15 **Fig 5B**		W15vsC15 W15vsS15 W15vsW11 >2	
Dscam	N/D		W11vsC11 W15vsC15 W15vsS15	In the ENS, HSCR locus[50]
Dcc	N/D		W11vsC11 W15vsC15 W15vsS15	In the ENS[51]
Neuregulin signaling				Studied in ENS[18]
***Nrg1*^ENS**	ENS and mesenchyme E13-E15, **S5**		W15vsC15 W15vsS15	In mesenchyme[52] HSCR locus[53] In adult ENS[54]
***Nrg3*^ENS**	N/D		W15vsC11 S15vsC15 W15vsW11 >4.5-6.2	HSCR locus[55, 56]
Erbb3	ENS E13-15		W11vsC11 W15vsC15 S15vsW15	In the ENS[52]
Neurotrophin signaling				Well-studied in ENS[57]
Bdnf	mesenchyme E14		C11vsS11 C15vsS15	In the gut[58]
***Ntf3* (*Nt3*)**	mesenchyme E11-E15		C11vsW11 C15vsW15	In mesenchyme[59]
Ntf5* **(*Nt4*)**	General gut E14 **S5**		C15vsW15	

Ngf*	N/D		C15vsW15 >2,5	In adult ENS[60]
***Ntrk2* (TrkB)**	Few ENS cells? E14			In the ENS (E16)[61]
***Ntrk3* (TrkC)**	Mesenchyme and ENS? E14		W15vsS15 W15vsW11	In the ENS[59]
***Ngfr* (p75)**	ENS E11-15		W11vsC11 W15vsC15	In the ENS[17]
Notch signaling				Studied in ENS[62]
Dll1	ENS E11-E15		W11vsC11 W15vsC15	In the ENS, [62]
Dll3	N/D		W15vsC15 S15vsW15 S11vsC11	In the ENS[62, 63]
Dll4	N/D		N/D	In the ENS[62]
Jag1	mesenchyme, ENS? E14		S15vsW15 W11vsW15 W15vsC15	In the ENS[62]
Notch1	General gut incl. ENS E11-15		S11vsC11 S15vsC15	In the ENS[62]
Notch2*	General gut incl. ENS E11-E14 **S5**		S11vsC11 S15vsS11 S15vsW15	
Notch4	N/A			In the ENS[62]
Prokineticin signaling				Studied in ENS[64]
Prok-1	N/D		N/D	In the mesenchyme[64]
Prokr1	N/D		W15vsS15 W15vsW11	In the ENS[64]
RA signaling				Studied in ENS[65]
Rara	General gut incl. ENS E11-14		S11vsC11 S15vsC15	In the ENS[65]
Rarb	ENS E15		S11vsC11 W15vsC15	In the ENS[27, 65]
Rarg	General gut incl. ENS E13-15		N/D	In the ENS[65]
Rxra	General gut incl. ENS E11-15		W11vsC11 C15vsW15	In the ENS[65]
Rxrb	General gut incl. ENS E11-14		N/D	In the ENS[65]
Rxrg	General gut incl. ENS E11-14		W11vsW15	In the ENS[65]
Semaphorin signaling				Sema3 studied in ENS[66]
Sema3a	mesenchyme E11-15		C11vsW11 C15vsW15	In the bowel[66] HSCR locus[67]
Sema3b*	mucosa and ENS E14-E15 **S5**		W15vsC15 S11vsC11 S15vsC15 >1,25-1,45	
Sema3c	mucosa and ENS E11-15		S11vsW11 W15vsC15	In the ENS[68]
Sema3d	mesenchyme		W11vsC11	In the ENS[68]

	ENS E11-15		C15vsW15	
Sema4d*	ENS E15 **Fig 5B**		W15vsC15 W15vsW11	Comment: Function in CNS[69]
Sema4f*	ENS E14 **S5**		W15vsC15 W15vsW11 S15vsC15	
Sema4g*	ENS E14 **S5**		W15vsC15 W15vsS15	
Sema5a*	mesenchyme E11-15, **S5**		C11vsW11 C15vsW15	
Sema6a*	ENS E13-15 **S5**		W15vsW11 W15vsS15	
Sema6d*	mesenchyme E11-15, **S5**		C15vsW15 W15vsW11	
Plxna1	mesenchyme E15		C15vsW15	In the ENS[68]
Plxna2	ENS E15		C11vsW11 W15vsC15	In the ENS[68]
Plxna3	ENS E13-15		W15vsC15 W15vsS15	In the ENS[68]
Plxna4	N/D		W11vsC11 W15vsC15 W15vsS15 >4-9	In the ENS[68]
Plxnb1*	mesenchyme and ENS E13-15	**In the ENS, Fig. 5B, 6; S6**	W11vsC11 W15vsC15 W15vsW11	
Plxnb3*	N/D		W15vsC15 S15vsC15 W15vsW11 >1,3-1,5	
Nrp1	ENS E11-15		W11vsC11 W11vsW15	In the ENS[68]
Nrp2	ENS E14		W15vsW11	In the ENS[68]
***L1cam* (co-receptor**	ENS E11-15		W11vsC11 W15vsS15	In the ENS[66]
***Nrcam* (co-receptor)**	ENS E11-15		W11vsC11 W15vsC15	In the chick ENS[70]
Slit signaling				Studied in ENS[71]
Slit1	ENS and mesenchyme E14-15		W15vsC15 W15vsW11	In the bowel wall[71]
Slit2	ENS and mesenchyme E14		C11vsW11 W15vsW11	In the ENS[71]
Slit3	ENS and mesenchyme E14		W11vsC11 W15vsC15	In the bowel wall[71]
Robo2	mesenchyme, hindgut mucosa E14		C11vsW11 C15vsW15 W15vsS15	In chick ENS[72]
***Slitrk signaling**				Comment: Function in CNS[73-75]
Bdnf	mesenchyme E14		C11vsS11 C15vsS15	Comment: Slitrk5 enhance TrkB

	S5			mediated signaling triggered by BDNF[74]
Ptprd*	mesenchyme and ENS **Fig 5B**		C11vsW11 C15vsW15	
Ptpro*	ENS E14 **S5**		W11vsC11 W15vsC15 W15vsS15	
Slitrk1*	ENS E13-15 **S5**		W15vsC15	
Slitrk2*	ENS? E14	**In the ENS Fig 6; S7**	W11vsC11 W15vsC15	
Slitrk3*	ENS and mesenchyme, E14	**In the ENS Fig. 5B, 6; S6, 7**	W15vsC15	
Slitrk5*	whole gut incl. ENS E14 **S5**		W15vsC15 W15vsW11	
Slitrk6	ENS and muscle E14		W11vsC11 W15vsC15	In the bowel wall[76]
TGFβ signaling				Comment: Function in CNS[77]
Tgfb1*	mesenchyme E11-15, **S5**		C11vsW11 C15vsW15	
Tgfb2	ENS E14-15	**In the ENS Fig 5B, 6; S6, 7**	W11vsC11 W15vsC15 S15vsS11	In the ENS[27]
Tgfb3*	serosa and mesenchyme E14, **S5**		C11vsW11 C15vsW15	
Tgfbr1*	Gut wall and mucosa, E14	**In the ENS; Fig 6; S6, 7**		
Tgfbr2*	Gut wall E14	**In the ENS, Fig 5B, 6; S6, 7**	C15vsW15	
Wnt signaling (canonical*)				Non-canonical pathway is studied in ENS[78]
Wnt2b* (Canonical)	serosa and mesenchyme E11-15 **Fig. 5D**		C11vsW11 C15vsW15 W11vsW15	In the adult gut[79]
Wnt4	Hindgut mucosa E11-15		C11vsW11 C15vsW15	In mucosa[80]
Wnt5a	mesenchyme E11-15		C11vsW11 C15vsW15 W11vsW15	In mesenchyme[80]
Wnt5b	mesenchyme E13		C11vsW11 C15vsW15	In serosa[80]
Wnt6	Esophagus E14			In serosa[80]
Wnt11	Esophagus E14		C11vsW11	In mesenchyme[80]
Lrp5* (Canonical)	ENS E11-14 **Fig. 5D**		W11vsC11 S11vsC11	

			S11vsS15	
Fzd3	ENS E11-15		W11vsC11 W15vsC15	In the ENS[78]
Celsr2*	ENS E14-15 **S5**		S11vsC11 S15vsC15	Comment: Function in non-canonical Wnt signaling[81]
Celsr3	ENS 13-15		S11vsC11 S15vsC15	In the ENS[78]
Receptors-Miscellaneous				
Lrp8*	ENS E14, **S5**		W15vsC15	
Lrp11*	ENS E15	**In the ENS** **S6, 7**	W15vsC15 S15vsS15	
Ptprg*	N/D		W11vsC11 W15vsC15 W15vsS15 >1,45	
Ptprj*	N/D		S11vsC11 S15vsC15 S15vsW15 >1,5	
Ptprm*	Mesenchyme and ENS E14 **S5**		S11vsC11 S15vsW15	
Ptprn*	ENS E14 **S5**		W11vsC11 W15vsS15	
Ptprn2*	N/D		W15vsC15 W15vsW15 W15vsS15 >1,8	
Ptprr*	N/D		W11vsC11 W15csS15 W15vsW11 >4,5	
Ptprs*	ENS E14 **S5**		W15vsC15 W15vsW11	

Supplementary Table 7. Up-to-date list of signaling factors (ligands and receptors) identified in or around the developing ENS.
Note that ligand-receptor interactions suggested in this table are based on experiments in other tissue.
*: genes previously not described in the developing mouse ENS. Expression was confirmed by IHC and/or convincing staining in online expression resources (bold black text). Enrichment in enteric populations of >2 and/or significant enrichment in at least 3 enteric populations were also considered as validation when quality was suboptimal in Online Expression Resources. Online ISH Resources = Allen Brain Atlas and GenePaint. ISH= *In situ* Hybridisation; IHC= Immunohistochemistry; S: Supplementary Figure; N/D: no (or suboptimal) data; HSCR: Hirschsprung disease

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