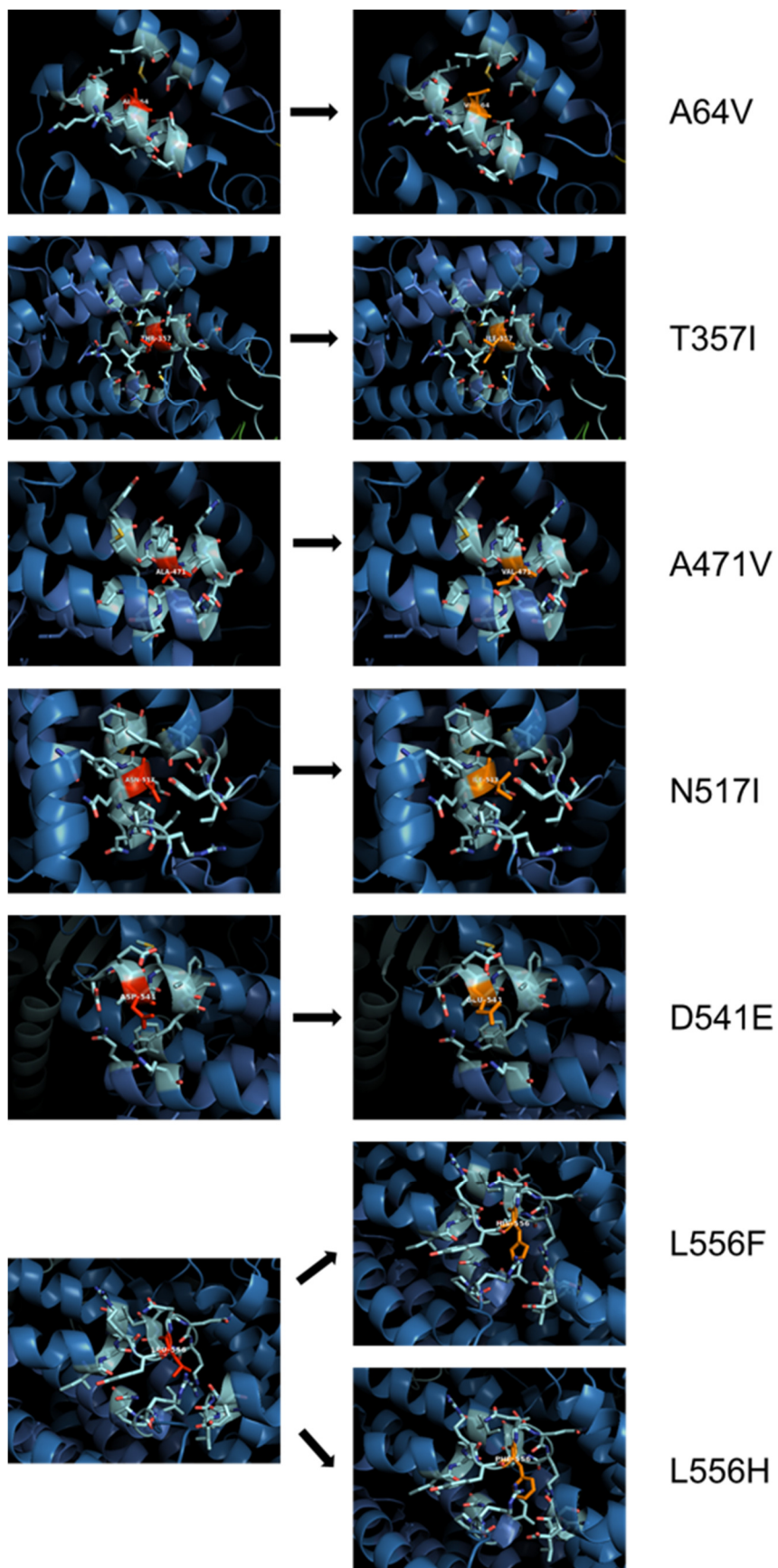


1 **Supplementary information**

2 **Figure S1: Illustration of suppressor mutations**

3 Each residue mutated in a suppressed SEP-1 is illustrated in both its wild-type as well as mutant
4 form. The residues within 6 angstroms of each residue are also depicted to provide a structural
5 context for each mutation. A general trend observed is that the suppressor mutations introduce
6 larger residues that have the potential to make new intramolecular contacts. Two alanine to
7 valine mutations at positions 64 and 471 reduce the distance to other non-polar residues. A64V
8 brings the distance to L376 from 5.6 to 4 Å and A417V lowers the distance to F476 and F454
9 from 4.6 and 5.6 Å to 3.3 and 4.4 Å, respectively. Two mutations that replace polar residues with
10 isoleucine have the potential to create new hydrophobic interactions. T357I brings the residue to
11 within 4.2 Å and N517I brings the residue within 4.8 Å of I552 and 4.7 Å of L556. A mutation
12 that preserves residue charge (D541E) reduces the distance from the basic residue (K482) from
13 4.3 to 4.2 Å. L556 mutations to histidine creates the potential for a new interaction with E160
14 while L556F brings R551 within 2.5 Å, potentially allowing a cation- π interaction. Images and
15 measurements were generated using PyMOL Molecular Graphics System from Schrödinger,
16 LLC.



18 Table S1: List of Strains

Strain	Mutation	Genotype	Isolation Frequency
WH408	SEP-1 (C450Y)	<i>sep-1(e2406) l/hT2g [bli-4(e937) let-?(q782) qIs48] (I;III)</i>	N/A
JAB54	SEP-1 (C450Y A64V)	<i>sep-1(e2406erb14) l</i>	2
JAB53	SEP-1 (C450Y T357I)	<i>sep-1 (e2406erb16) l</i>	1
JAB76	SEP-1 (C450Y V392I)	<i>sep-1(e2406erb27) l</i>	1
JAB126	SEP-1 (C450Y A471V)	<i>sep-1(e2406erb29) l</i>	1
JAB50	SEP-1 (C450Y N517I)	<i>sep-1 (e2406erb17) l</i>	1
JAB58	SEP-1 (C450Y D541E)	<i>sep-1(e2406erb15) l</i>	1
JAB51	SEP-1 (C450Y L556H)	<i>sep-1 (2406erb10) l</i>	2
JAB45	SEP-1 (C450Y L556F)	<i>sep-1(e2406erb5) l</i>	4
JAB46	SEP-1 (C450Y L556F)	<i>sep-1(e2406erb6) l</i>	4
JAB47	SEP-1 (Y450C)	<i>sep-1(erb7) l</i>	1
JAB48	SEP-1 (C450Y L556F)	<i>sep-1(e2406erb8) l</i>	4
JAB49	SEP-1 (C450Y L556F)	<i>sep-1(e2406erb9) l</i>	4
JAB61	SEP-1 (C450Y L556H)	<i>sep-1(e2406erb18) l</i>	2
JAB64	SEP-1 (C450Y A64V)	<i>sep-1(e2406erb19) l</i>	2
JAB106	SEP-1 (C450Y); PPH-5 (I32N)	<i>sep-1(e2406) l; pph-5(erb58) V</i>	1
JAB97	SEP-1 (C450Y); PPH-5 (Y52H)	<i>sep-1(e2406) l; pph-5(erb47) V</i>	1
JAB99	SEP-1 (C450Y); PPH-5 (G66E)	<i>sep-1(e2406) l; pph-5(erb51) V</i>	1
JAB65	SEP-1 (C450Y); PPH-5 (Y72*)	<i>sep-1(e2406) l; pph-5(erb20) V</i>	2
JAB94	SEP-1 (C450Y); PPH-5 (L77P)	<i>sep-1(e2406) l; pph-5(erb44) V</i>	1
JAB103	SEP-1 (C450Y); PPH-5 (S105F)	<i>sep-1(e2406) l; pph-5(erb54) V</i>	1
JAB79	SEP-1 (C450Y); PPH-5 (M211K)	<i>sep-1(e2406) l; pph-5(erb30) V</i>	1
JAB96	SEP-1 (C450Y); PPH-5 (H243R)	<i>sep-1(e2406) l; pph-5(erb46) V</i>	1
JAB95	SEP-1 (C450Y); PPH-5 (G244E)	<i>sep-1(e2406) l; pph-5(erb45) V</i>	1
JAB80	SEP-1 (C450Y); PPH-5 (D270A)	<i>sep-1(e2406) l; pph-5(erb31) V</i>	1
JAB67	SEP-1 (C450Y); PPH-5 (D270N)	<i>sep-1(e2406) l; pph-5(erb57) V</i>	1
JAB98	SEP-1 (C450Y); PPH-5 (M285R)	<i>sep-1(e2406) l; pph-5(erb48) V</i>	1
JAB111	SEP-1 (C450Y); PPH-5 (R300C)	<i>sep-1(e2406) l; pph-5(erb63) V</i>	2
JAB66	SEP-1 (C450Y); PPH-5 (N309K)	<i>sep-1(e2406) l; pph-5(erb21) V</i>	1
JAB107	SEP-1 (C450Y); PPH-5 (M311R)	<i>sep-1(e2406) l; pph-5(erb59) V</i>	1
JAB91	SEP-1 (C450Y); PPH-5 (Y322I)	<i>sep-1(e2406) l; pph-5(erb42) V</i>	1
JAB120	SEP-1 (C450Y); PPH-5 (S397P)	<i>sep-1(e2406) l; pph-5(erb68) V</i>	1
JAB72	SEP-1 (C450Y); PPH-5 (W413G)	<i>sep-1(e2406) l; pph-5(erb33) V</i>	1
JAB88	SEP-1 (C450Y); PPH-5 (C414Y)	<i>sep-1(e2406) l; pph-5(erb38) V</i>	1
JAB77	SEP-1 (C450Y); PPH-5 (H426Q)	<i>sep-1(e2406) l; pph-5(erb28) V</i>	1
JAB70	SEP-1 (C450Y); PPH-5 (C441Y)	<i>sep-1(e2406) l; pph-5(erb22) V</i>	1
JAB117	SEP-1 (C450Y); PPH-5 (T443I)	<i>sep-1(e2406) l; pph-5(erb65) V</i>	1

JAB89	SEP-1 (C450Y); PPH-5 (P448L)	<i>sep-1(e2406) l; pph-5(erb40) V</i>	1
JAB100	SEP-1 (C450Y); PPH-5 (G458E)	<i>sep-1(e2406) l; pph-5(erb52) V</i>	2
JAB121	SEP-1 (C450Y); PPH-5 (A471*)	<i>sep-1(e2406) l; pph-5(erb69) V</i>	1
JAB122	SEP-1 (C450Y); PPH-5 (H351R)	<i>sep-1(e2406) l; pph-5(erb70) V</i>	2
JAB124	SEP-1 (C450Y); PPH-5 (H351R)	<i>sep-1(e2406) l; pph-5(erb72) V</i>	2
JAB55	Splice site acceptor (<i>pph-5</i> intron 6)	<i>sep-1(e2406) l; pph-5(erb11) V</i>	1
JAB56	Splice site donor (<i>pph-5</i> intron 3)	<i>sep-1(e2406) l; pph-5(erb12) V</i>	1
JAB57	SEP-1 (C450Y); PPH-5 (Y65* Y72*)	<i>sep-1(e2406) l; pph-5(erb13) V</i>	1
JAB73	250 bp deletion (<i>pph-5</i> exon 1-2)	<i>sep-1(e2406) l; pph-5(erb25) V</i>	1
JAB75	Splice site donor (<i>pph-5</i> intron 1)	<i>sep-1(e2406) l; pph-5(erb26) V</i>	1
JAB85	32bp deletion (<i>pph-5</i> exon 1)	<i>sep-1(e2406) l; pph-5(erb32) V</i>	1
JAB62	SEP-1 (C450Y A471V); PPH-5 (L384F)	<i>sep-1(e2406 erb29) l; pph-5(erb34) V</i>	1
JAB86	Repetitive region of <i>pph-5</i>	<i>sep-1(e2406) l; pph-5(erb35) V</i>	1
JAB63	SEP-1 (C450Y); PPH-5 (Y72*)	<i>sep-1(e2406) l; pph-5(erb36) V</i>	2
JAB69	Splice site acceptor (<i>pph-5</i> intron 7)	<i>sep-1(e2406) l; pph-5(erb39) V</i>	1
JAB90	SEP-1 (C450Y); PPH-5 (Q245*)	<i>sep-1(e2406) l; pph-5(erb41) V</i>	1
JAB93	SEP-1 (C450Y); PPH-5 (Q389*)	<i>sep-1(e2406) l; pph-5(erb43) V</i>	1
JAB125	Deletion of <i>pph-5</i> exon 4 & 5	<i>sep-1(e2406) l; pph-5(erb49) V</i>	1
JAB127	Deletion of <i>pph-5</i> exon 5	<i>sep-1(e2406) l; pph-5(erb50) V</i>	1
JAB102	SEP-1 (C450Y); PPH-5 (R300C)	<i>sep-1(e2406) l; pph-5(erb53) V</i>	1
JAB104	Splice site acceptor (<i>pph-5</i> intron 1)	<i>sep-1(e2406) l; pph-5(erb55) V</i>	1
JAB105	SEP-1 (C450Y); PPH-5 (G458E)	<i>sep-1(e2406) l; pph-5(erb56) V</i>	2
JAB109	98bp deletion (<i>pph-5</i> exon 3)	<i>sep-1(e2406) l; pph-5(erb61) V</i>	1
JAB110	Splice site acceptor (<i>pph-5</i> intron 1)	<i>sep-1(e2406) l; pph-5(erb62) V</i>	1
JAB112	SEP-1 (C450Y); PPH-5 (L384F)	<i>sep-1(e2406) l; pph-5(erb64) V</i>	1
JAB123	SEP-1 (C450Y); HSP-90 (M661K)	<i>sep-1(e2406) l; hsp-90(erb71) V</i>	1
JAB136	HSP-90 (M661K)	<i>hsp-90(erb71) V</i>	N/A
JAB78	SEP-1 (C450Y); unk	<i>sep-1(e2406) l; erb23</i>	1
JAB59	SEP-1 (C450Y); unk	<i>sep-1(e2406) l; erb24</i>	1
JAB87	SEP-1 (C450Y); unk	<i>sep-1(e2406) l; erb37</i>	1
JAB108	SEP-1 (C450Y); unk	<i>sep-1(e2406) l; erb60</i>	1
JAB118	SEP-1 (C450Y); unk	<i>sep-1(e2406) l; erb66</i>	1
JAB119	SEP-1 (C450Y); unk	<i>sep-1(e2406) l; erb67</i>	1
WH410	SEP-1 (H738P)	<i>sep-1(ax110) l/hT2g [bli-4(e937) let-?(q782) qIs48] (I;III)</i>	N/A
JAB42	SEP-1 (H738P); PPH-5(S229L)	<i>sep-1(ax110) l; pph-5(erb1) V</i>	1
JAB43	SEP-1 (H738P); PPH-5(M380T)	<i>sep-1(ax110) l; pph-5(erb2) V</i>	1
JAB44	SEP-1 (H738P); PPH-5(L77P)	<i>sep-1(ax110) l; pph-5(erb3) V</i>	2

JAB92	SEP-1 (H738P); PPH-5(L77P)	<i>sep-1(ax110)</i> l; <i>pph-5(erb4)</i> V	2
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Table S2: List of primers used for single worm PCR and sequencing of *sep-1*

Primer	Target	Sequence*	Direction
oASP-UTK3	<i>sep-1(ax110)</i>	GTCGTCCGAAAAGTTGAGAACTGG	F
oASP-UTK4	<i>sep-1(ax110)</i>	TGCATCAGCGGCAGGAACGATT	R
oASP-UTK7	<i>sep-1(e2406)</i>	ctgagacatcacacgaaagc	F
oASP-UTK8	<i>sep-1(e2406)</i>	GAGTTGTCGTCCAAGTTGTG	R
oASP-UTK9	<i>sep-1</i> FL	ATGAAGATCACAAACAAGTCAG	F
oASP-UTK10	<i>sep-1</i> FL	TTACAAATTTCTGGGATCTTGATGG	R
oASP-UTK11	<i>sep-1</i> FL-seq	AATCGTTCCTGCCGCTGATGCA	F
oASP-UTK12	<i>sep-1</i> FL-seq	cagCTTTATTGGACATGGCTCTGGA	F
oASP-UTK13	<i>sep-1</i> exon 1	gaagataacgtgcgttgaaacc	F
oASP-UTK14	<i>sep-1</i> exon 3	ccgtctctgtagggtcaaattc	R
oASP-UTK28	<i>sep-1(ax110)</i>	aaaatcaaattctaccgagcg	F
oASP-UTK29	<i>sep-1(ax110)</i>	gcatcaaataagggtgcgaaatac	R
oASP-UTK30	<i>sep-1(ax110)</i>	GTCGTCCGAAAAGTTGAGAACT	F
oASP-UTK34	<i>sep-1(e2406)</i>	gtagatttacggcgctttgc	F
oASP-UTK46	<i>sep-1</i> exon 4	ctgagacatcacacgaaagcc	F
oASP-UTK47	<i>sep-1</i> exon 8	AGAGCCATGTCCAATAAAGctg	R
oASP-UTK48	<i>sep-1</i> exon 7	GAGAAGTTCAAATCGTTCCTGCC	F
oASP-UTK54	<i>sep-1</i> seq primer	TCCAGAGCCATGTCCAATAAAGctg	R

* nucleotides found in exons are in uppercase while intronic nucleotides are in lowercase

Table S3: List of primers used for single worm PCR and sequencing of *pph-5*

Primer	Target	Sequence*	Direction
oASP-UTK15	<i>pph-5</i> exon1-2	gggttaaattttagggaaccgc	F
oASP-UTK16	<i>pph-5</i> exon1-2	cgaaattttctttaaccggg	R
oASP-UTK17	<i>pph-5</i> exon 3	gctgctaattcaattttgggc	F
oASP-UTK18	<i>pph-5</i> exon 3	tgccggttttacatcaattttc	R
oASP-UTK19	<i>pph-5</i> exon 4	gaaaacgtgcaaatttccaatc	F
oASP-UTK20	<i>pph-5</i> exon 4	cctcaattttcagctgttttg	R
oASP-UTK21	<i>pph-5</i> exon 5	gaaaatggcctaattttcac	F
oASP-UTK22	<i>pph-5</i> exon 5	aggatttcagcgatttctgg	R
oASP-UTK24	<i>pph-5</i> exon 6	cagattattgattttcccgacag	R
oASP-UTK26	<i>pph-5</i> exon 8	ctgaaattgcttgtaaagcctc	F
oASP-UTK27	<i>pph-5</i> exon 8	tggaagagattttcgtttcgtg	R
oASP-UTK35	<i>pph-5</i> exon 7	tgatttcagctcaaaattaacg	F
oASP-UTK37	<i>pph-5</i> exon 7	cagtgcgatttcttacCGTC	R
oASP-UTK38	<i>pph-5</i> exon 6	cagGTGTGCCATGGTGGATT	F
oASP-UTK39	<i>pph-5</i> exon 6	cagccattttctacaaacctacC	R

oASP-UTK40	<i>pph-5</i> exon 8	caattttcagCCCCGATTCACG	F
oASP-UTK41	<i>pph-5</i> exon 8	taggcctaactcggcCTAATT	R
oASP-UTK50	<i>pph-5</i> exon 5	Aggatttcagcgatttctgggc	R
oASP-UTK51	<i>pph-5</i> exon 6	ggtatttttccagGTGTGCCATGG	F
oASP-UTK52	<i>pph-5</i> exon 7	gcagtgcgatttcttacCGTC	R
oASP-UTK53	<i>pph-5</i> exon 5	ccgaaaatggccaaattttcac	F

* nucleotides found in exons are in uppercase while intronic nucleotides are in lowercase

Table S4: List of primers used for single worm PCR and sequencing of *hsp-90*

Primer	Target	Sequence*	Direction
oASP-UTK60	<i>hsp-90</i>	ATGTCCGAGAACGCCGAAAC	F
oASP-UTK61	<i>hsp-90</i>	aggatgtTAGTCGACCTCCTCC	R
oASP-UTK62	<i>hsp-90</i> seq	GTATTCTGGCATGAGCTCTTCG	R
oASP-UTK63	<i>hsp-90</i> seq	CACAAAGAGCTCCATTGATCTC	F

* nucleotides found in exons are in uppercase while intronic nucleotides are in lowercase

Table S5: List of all *sep-1(e2406)* suppressing *pph-5* lesions

Pph-5 allele	Nucleotide change	Effect
<i>pph-5(erb11)</i>	G>A	Splice site acceptor intron 6
<i>pph-5(erb12)</i>	30 bp deletion spanning exon 3 and intron 3	splice site donor intron 3
<i>pph-5(erb13)</i>	G>A, T>A	Y65*, Y72*
<i>pph-5(erb20)</i>	T>G	Y72*
<i>pph-5(erb21)</i>	G>A	N309K
<i>Pph-5(erb22)</i>	G>A	C441Y
<i>pph-5(erb25)</i>	250 bp deletion in exon 1-2	Frameshift, early stop
<i>pph-5(erb26)</i>	T>A	Splice site donor exon 1
<i>pph-5(erb28)</i>	T>A	H426Q
<i>pph-5(erb30)</i>	T>A	M211K
<i>pph-5(erb31)</i>	A>C	D270A
<i>pph-5(erb32)</i>	32 bp deletion in exon1	Frameshift, early stop
<i>pph-5(erb33)</i>	T>G	W413G
<i>pph-5(erb34)</i>	C>T	L384F
<i>pph-5(erb36)</i>	T>G	Y72*
<i>pph-5(erb38)</i>	G>A	C414Y
<i>pph-5(erb39)</i>	G>A	Splice site acceptor, exon 7
<i>pph-5(erb40)</i>	C>T	P448L
<i>pph-5(erb41)</i>	C>T	Q245*
<i>pph-5(erb42)</i>	1 bp deletion in exon 5	Y322I, Frameshift early stop

<i>pph-5(erb43)</i>	C>T	Q389*
<i>pph-5(erb44)</i>	C>T	L77P
<i>pph-5(erb45)</i>	G>A	G244E
<i>pph-5(erb46)</i>	A>G	H243R
<i>pph-5(erb47)</i>	T>A	Y52H
<i>pph-5(erb48)</i>	T>G	M285R
<i>pph-5(erb49)</i>	Deletion	Loss of exon 4 and 5
<i>pph-5(erb50)</i>	Deletion	Loss of exon 5
<i>pph-5(erb51)</i>	G>A	G66E
<i>pph-5(erb52)</i>	C>T	G458E
<i>pph-5(erb53)</i>	C>T	R300C
<i>pph-5(erb54)</i>	C>T	S105F
<i>pph-5(erb55)</i>	G>A	Splice site acceptor exon 2
<i>pph-5(erb56)</i>	G>A	G458E
<i>pph-5(erb57)</i>	G>A	D270N
<i>pph-5(erb58)</i>	T>A	I32N
<i>pph-5(erb59)</i>	T>G	M311R
<i>pph-5(erb61)</i>	98 bp deletion in exon 3	Frameshift early stop
<i>pph-5(erb62)</i>	G>A	Splice site acceptor exon 2
<i>pph-5(erb63)</i>	C>T	R300C
<i>pph-5(erb64)</i>	C>T	L384F
<i>pph-5(erb65)</i>	C>T	T443I
<i>pph-5(erb68)</i>	T>C	S397P

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