

Supplemental Information:

Genetic variation across RNA metabolism and cell death gene networks is implicated in the semantic variant of primary progressive aphasia

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SUPPLEMENTAL TABLES

Supplementary Table S1. Full PINBPA Results

Gene Name	Chromosome	Description	Ensembl ID	HGNC ID	HPRD ID	MIM ID	Gene P-value	snpP-value
HAP1	17	huntingtin-associated protein 1	ENSG00000173805	4812	2972	600947	6.13E-03	3.55E-03
ZNHIT3	17	"zinc finger, HIT type 3"	ENSG00000108278	12309	5139	604500	1.11E-03	9.79E-05
NFIX	19	nuclear factor I/X (CCAAT-binding transcription factor)	ENSG00000008441	7788	1234	164005	9.94E-04	1.74E-03
SKIL	3	SKI-like oncogene	ENSG00000136603	10897	1319	165340	2.65E-03	8.90E-04
TRIM41	5	tripartite motif-containing 41	ENSG00000146063	19013	15558	610530	5.40E-04	9.65E-03
SMAD4	18	SMAD family member 4	ENSG00000141646	6770	2995	600993	0.02	0.01
SMAD3	15	SMAD family member 3	ENSG00000166949	6769	4380	603109	0.04	1.06E-04
NBL1	1	"neuroblastoma, suppression of tumorigenicity 1"	ENSG00000158747	7650	9001	600613	0.03	5.30E-03
PACS1	11	phosphofurin acidic cluster sorting protein 1	ENSG00000175115	30032	6320	607492	0.01	1.75E-03
MYBL2	20	v-myb myeloblastosis viral oncogene homolog (avian)-like 2	ENSG00000101057	7548	3247	601415	0.04	0.02
E2F3	6	E2F transcription factor 3	ENSG00000112242	3115	2693	600427	0.04	8.32E-04
MED15	22	mediator complex subunit 15	ENSG00000099917	14248	12117	607372	0.01	2.45E-03
EBI3	19	Epstein-Barr virus induced 3	ENSG00000105246	3129	12051	605816	0.02	8.82E-03
SUB1	5	SUB1 homolog (S. cerevisiae)	ENSG00000113387	19985	2737	600503	0.03	4.64E-03
PELP1	17	"proline, glutamate and leucine rich protein 1"	ENSG00000141456	30134	10144	609455	0.01	4.38E-03
MECR	1	mitochondrial trans-2-enoyl-CoA reductase	ENSG00000116353	19691	12192	608205	0.02	1.61E-03
FHL3	1	four and a half LIM domains 3	ENSG00000183386	3704	9101	602790	0.04	2.52E-03
RIT1	1	Ras-like without CAAX 1	ENSG00000143622	10023	10195	609591	0.03	8.67E-03
NR6A1	9	"nuclear receptor subfamily 6, group A, member 1"	ENSG00000148200	7985	4147	602778	0.03	9.15E-03
ARFRP1	20	ADP-ribosylation factor related protein 1	ENSG00000101246	662	5264	604699	1.19E-03	1.83E-04

TFDP1	13	transcription factor Dp-1	ENSG00000198176	11749	1792	189902	9.54E-03	1.22E-04
THSD7A	7	"thrombospondin, type I, domain containing 7A"	ENSG00000005108	22207		612249	0.03	8.04E-05
UBE2I	16	"ubiquitin-conjugating enzyme E2I (UBC9 homolog, yeast)"	ENSG00000103275	12485	9045	601661	1.89E-04	5.23E-04
AKT1	14	v-akt murine thymoma viral oncogene homolog 1	ENSG00000142208	391	1261	164730	0.01	0.02
NCOR1	17	nuclear receptor co-repressor 1	ENSG00000141027	7672	2911	600849	0.04	0.04
GTF2B	1	general transcription factor IIB	ENSG00000137947	4648	8928	189963	0.01	8.76E-03
PSEN1	14	presenilin 1	ENSG00000080815	9508	87	104311	0.03	6.29E-03
BATF	14	"basic leucine zipper transcription factor, ATF-like"	ENSG00000156127	958	9820	612476	0.04	1.16E-03
PPL	16	periplakin	ENSG00000118898	9273	4187	602871	0.01	1.45E-04
HNF4A	20	"hepatocyte nuclear factor 4, alpha"	ENSG00000101076	5024	2612	600281	2.48E-03	3.96E-04
SLC2A4	17	"solute carrier family 2 (facilitated glucose transporter), member 4"	ENSG00000181856	11009	688	138190	1.60E-03	2.64E-03
FSTL3	19	folliculin-like 3 (secreted glycoprotein)	ENSG00000070404	3973	5632	605343	5.45E-04	3.60E-04
EP300	22	E1A binding protein p300	ENSG00000100393	3373	4078	602700	0.04	6.22E-03
MRPL30	2	mitochondrial ribosomal protein L30	ENSG00000185414	14036	14751	611838	0.02	0.02
RAD23A	19	RAD23 homolog A (S. cerevisiae)	ENSG00000179262	9812	7191	600061	9.94E-04	2.67E-03
TAL1	1	T-cell acute lymphocytic leukemia 1	ENSG00000162367	11556	1753	187040	0.02	0.01
ZNF622	5	zinc finger protein 622	ENSG00000173545	30958	12278	608694	5.47E-03	9.54E-04
HMOX2	16	heme oxygenase (decycling) 2	ENSG00000103415	5014	783	141251	7.45E-03	2.42E-03
C19orf50	19		ENSG00000105700	28420	14526		0.01	6.44E-03
NFIL3	9	"nuclear factor, interleukin 3 regulated"	ENSG00000165030	7787	5619	605327	0.04	0.01
KRT81	12	keratin 81	ENSG00000205426	6458	3691	602153	3.16E-04	2.07E-05
PLK2	5	polo-like kinase 2 (Drosophila)	ENSG00000145632	19699	6118	607023	0.01	3.97E-03

PKN2	1	protein kinase N2	ENSG00000065243	9406	3972	602549	0.01	5.05E-03
RALA	7	v-ral simian leukemia viral oncogene homolog A (ras related)	ENSG00000006451	9839	1549	179550	4.59E-04	3.49E-05
PSMD11	17	"proteasome (prosome, macropain) 26S subunit, non-ATPase, 11"	ENSG00000108671	9556	5119	604449	0.05	5.69E-04
TH1L	20	TH1-like (Drosophila)	ENSG00000101158	15934	16096	605297	0.01	1.45E-03
NUDCD3	7	NudC domain containing 3	ENSG00000015676	22208	13831	610296	0.03	8.04E-03
IFRD1	7	interferon-related developmental regulator 1	ENSG00000006652	5456	4612	603502	5.91E-03	2.19E-04
STAT6	12	"signal transducer and activator of transcription 6, interleukin-4 induced"	ENSG00000166888	11368	3302	601512	7.84E-03	7.55E-03
RANGAP1	22	Ran GTPase activating protein 1	ENSG00000100401	9854	3839	602362	8.51E-03	8.37E-03
SEC62	3	SEC62 homolog (S. cerevisiae)	ENSG00000008952	11846	3706	602173	2.65E-03	1.50E-03
SATB1	3	SATB homeobox 1	ENSG00000182568	10541	3647	602075	0.02	3.86E-04
YY1	14	YY1 transcription factor	ENSG00000100811	12856	2482	600013	0.04	0.03
MAML1	5	mastermind-like 1 (Drosophila)	ENSG00000161021	13632	5665	605424	8.61E-03	2.30E-03
TEF	22	thyrotrophic embryonic factor	ENSG00000167074	11722	1783	188595	8.51E-03	1.33E-03
MPP3	17	"membrane protein, palmitoylated 3 (MAGUK p55 subfamily member 3)"	ENSG00000161647	7221	3069	601114	0.03	0.01
JUN	1	jun oncogene	ENSG00000177606	6204	1302	165160	6.46E-03	4.57E-03
SS18	18	"synovial sarcoma translocation, chromosome 18"	ENSG00000141380	11340	2559	600192	1.82E-03	1.63E-03
MDH1	2	"malate dehydrogenase 1, NAD (soluble)"	ENSG00000014641	6970	1100	154200	1.09E-03	2.64E-04
NOTCH1	9	"Notch homolog 1, translocation-associated (Drosophila)"	ENSG00000148400	7881	1827	190198	2.65E-03	3.28E-03
NR5A1	9	"nuclear receptor subfamily 5, group A, member 1"	ENSG00000136931	7983	1702	184757	0.03	9.15E-03
PIAS3	1	"protein inhibitor of activated STAT, 3"	ENSG00000131788	16861	9068	605987	0.04	0.03

IRF4	6	interferon regulatory factor 4	ENSG00000137265	6119	3543	601900	5.40E-04	7.75E-05
THADA	2	thyroid adenoma associated	ENSG00000115970	19217	18177	611800	0.01	3.25E-04

Supplemental Table S1 Legend. Canonical name of gene SNPs, Band – chromosomal locationlocation, Block # – block association membership defined as groups of sequential genes with a p-value of <.05, Chrom – chromosomal location, ENSEMBL ID – annotation ID in ENSEMBL, HGNC ID – Human genome nomenclature ID, HPRD ID – Human protein reference database, MIMID – Mendelian inheritance in man ID, P-value – Gene p value, Top SNP p-value – Top p value for SNP

Supplementary Table S2. Full Expression Results in Pathologically Confirmed FTLD-U Cases

Gene Symbol	Beta	SE	P-Value	P-Value (FDR)
<i>AKT1</i>	-0.021	0.26	0.948	0.948
<i>ARFRP1</i>	-0.91	0.24	0.00657	0.0346
<i>BATF</i>	-0.92	0.256	0.00606	0.0346
<i>E2F3</i>	-0.492	0.53	0.128	0.226
<i>EBI3</i>	-0.952	0.375	0.00464	0.0299
<i>EP300</i>	-0.624	0.561	0.0561	0.136
<i>FHL3</i>	-0.398	0.257	0.217	0.331
<i>FSTL3</i>	-0.59	0.305	0.0703	0.157
<i>GTF2B</i>	0.675	0.393	0.0397	0.11
<i>HAP1</i>	-0.799	0.299	0.0159	0.0577
<i>HMOX2</i>	0.449	0.541	0.165	0.273
<i>HNF4A</i>	-1.53	0.195	0.0000216	0.00125
<i>IFRD1</i>	0.0831	0.733	0.795	0.863
<i>IRF4</i>	-0.664	0.0901	0.0428	0.113
<i>JUN</i>	0.0433	0.857	0.892	0.924
<i>KRT81</i>	-0.981	0.293	0.00363	0.0263
<i>MAML1</i>	-0.314	0.624	0.328	0.449
<i>MDH1</i>	0.365	0.75	0.256	0.363
<i>MECR</i>	0.0992	0.487	0.756	0.843
<i>MED15</i>	-0.376	0.198	0.242	0.36
<i>MPP3</i>	-0.265	1.12	0.408	0.504
<i>MYBL2</i>	-0.999	0.251	0.00313	0.0263
<i>NBL1</i>	0.0268	0.537	0.933	0.948
<i>NCOR1</i>	0.566	0.35	0.082	0.168
<i>NFIL3</i>	0.122	1.1	0.701	0.814
<i>NOTCH1</i>	0.0444	0.407	0.889	0.924
<i>NR5A1</i>	-1.31	0.199	0.000184	0.00355
<i>NR6A1</i>	-0.86	0.218	0.00989	0.0426
<i>NUDCD3</i>	0.115	0.443	0.718	0.816
<i>PACS1</i>	-0.855	0.192	0.0103	0.0426
<i>PELP1</i>	-0.871	0.246	0.00905	0.0426
<i>PIAS3</i>	0.147	0.356	0.646	0.765
<i>PKN2</i>	-0.723	0.69	0.0282	0.0962
<i>PLK2</i>	0.279	2.26	0.384	0.494
<i>PPL</i>	0.566	0.797	0.0819	0.168
<i>PSEN1</i>	1.04	0.605	0.00212	0.0246
<i>PSMD11</i>	0.296	0.281	0.356	0.469

<i>RAD23A</i>	0.371	0.374	0.249	0.361
<i>RALA</i>	0.626	0.316	0.0555	0.136
<i>RANGAP1</i>	-0.41	0.381	0.204	0.319
<i>RIT1</i>	0.465	0.451	0.15	0.256
<i>SATB1</i>	-0.511	0.763	0.115	0.208
<i>SEC62</i>	0.562	0.407	0.0841	0.168
<i>SKIL</i>	-0.69	0.0925	0.0357	0.11
<i>SLC2A4</i>	-1.16	0.237	0.000736	0.0107
<i>SMAD3</i>	0.59	0.292	0.0702	0.157
<i>SMAD4</i>	0.555	0.661	0.0881	0.17
<i>SS18</i>	0.674	0.59	0.0399	0.11
<i>STAT6</i>	-0.258	0.446	0.42	0.508
<i>SUB1</i>	0.685	0.521	0.0368	0.11
<i>TAL1</i>	-1.37	0.287	0.0000996	0.00289
<i>TEF</i>	-0.835	0.109	0.012	0.0465
<i>TFDP1</i>	-0.0795	0.389	0.803	0.863
<i>THADA</i>	0.522	0.239	0.108	0.202
<i>THSD7A</i>	0.433	0.62	0.179	0.289
<i>UBE2I</i>	-0.985	0.284	0.00351	0.0263
<i>YY1</i>	0.311	0.327	0.333	0.449
<i>ZNHIT3</i>	0.265	0.484	0.408	0.504

Supplementary Table S2 Legend. Expression analyses revealed 22 out of 64 genes in our SD network showed nominally significant dysregulated expression in pathologically confirmed cases of frontotemporal dementia with ubiquitinated inclusions (FTLD-U) vs age-matched controls.

Supplemental Figure 3: Gene level side by side comparison of 64 VEGAS identified genes with OMIM biological processes and previous implications in degenerative disease

Gene Name	Chr. #	Description	Ensembl ID	HGNC ID	HPRD ID	MIM ID	Top Snp	Gene P-value	Snp P-value	Braineac tID	Start Location	Stop Location	Number of Probe Sets	Region Rank 1	Region Rank 2	Region Rank 3	OMIM Biological Process	Degenerative Disease/Process Association
<i>AKT1</i>	14	v-akt murine thymoma viral oncogene homolog 1	ENSG00000142208	391	1261	164730	rs12432802	0.01	0.02	3581132	10523695	105262055	33	OCTX	FCTX	HIPP	Growth factor-induced neuronal survival	Alzheimer Disease, ¹ Frontotemporal dementia, ² Huntington Disease, ³ Parkinson Disease ⁴
<i>ARFRP1</i>	20	ADP-ribosylation factor related protein 1	ENSG00000101246	662	5264	604699	rs11696871	<0.01	<0.01	3914072	62330007	62339365	18	WHMT	OCTX	TCTX	Lipolysis	None reported
<i>BATF</i>	14	"basic leucine zipper transcription factor, ATF-like"	ENSG00000156127	958	9820	612476	rs175722	0.04	<0.01	3544605	75940385	76013335	7	PUTM	WHMT	FCTX	Hematopoietic stem cell transcription factor, Telomere length	None reported
<i>C19orf50</i>	19		ENSG00000105700	28420	14526	na	rs10854166	0.01	0.01	3825141	18668598	18680176	12	WHMT	MEDU	SNIG	Lysosomal function	Retinal Degeneration ⁵
<i>E2F3</i>	6	E2F transcription factor 3	ENSG00000112242	3115	2693	600427	rs746720	0.04	<0.01	2897576	20393801	20493940	11	HIPP	FCTX	PUTM	Cell cycle	Neuroinflammation ⁶
<i>EBI3</i>	19	Epstein-Barr virus induced 3	ENSG00000105246	3129	12051	605816	rs7253162	0.02	0.01	3817380	4229299	4244057	5	SNIG	WHMT	THAL	Immune regulation	Alzheimer Disease ⁷
<i>EP300</i>	22	E1A binding protein p300	ENSG00000100393	3373	4078	602700	rs5758211	0.04	0.01	3946615	41487790	41576079	44	CRBL	WHMT	OCTX	Cell proliferation and differentiation	None reported
<i>FHL3</i>	1	four and a half LIM domains 3	ENSG00000183386	3704	9101	602790	rs4440824	0.04	<0.01	2407478	38462445	38471310	6	MEDU	SNIG	WHMT	Immune regulation	None reported
<i>FSTL3</i>	19	folliculin-like 3 (secreted glycoprotein)	ENSG00000070404	3973	5632	605343	rs13730	<0.01	<0.01	3815097	674029	683385	8	WHMT	MEDU	HIPP	Cell proliferation and differentiation	None reported
<i>GTF2B</i>	1	general transcription factor IIB	ENSG00000137947	4648	8928	189963	rs11809597	0.01	0.01	2421753	89318321	89357607	9	FCTX	TCTX	OCTX	Transcription initiation and regulation	Huntington Disease, ⁸ Spinocerebellar ataxia, Machado-Joseph Disease ⁹
<i>HAP1</i>	17	huntingtin-associated protein 1	ENSG00000173805	4812	2972	600947	rs4796691	0.01	<0.01	3757288	39873994	39890926	16	SNIG	HIPP	MEDU	Cellular trafficking	Alzheimer Disease ¹⁰
<i>HMOX2</i>	16	heme oxygenase (decycling) 2	ENSG00000103415	5014	783	141251	rs1684600	0.01	<0.01	3678186	4558594	4588778	13	OCTX	THAL	FCTX	Heme degradation	None reported
<i>HNF4A</i>	20	hepatocyte nuclear factor 4, alpha	ENSG00000101076	5024	2612	600281	rs11699901	<0.01	<0.01	3886453	42984100	43061484	23	FCTX	SNIG	HIPP	Hepatic metabolism	Duchenne Muscular Dystrophy ¹¹
<i>IFRD1</i>	7	interferon-related developmental regulator 1	ENSG00000006652	5456	4612	603502	rs2520482	0.01	<0.01	3019519	112048229	112116552	19	WHMT	HIPP	SNIG	Cell proliferation and differentiation	Neuroinflammation ¹²
<i>IRF4</i>	6	interferon regulatory factor 4	ENSG00000137265	6119	3543	601900	rs6900384	<0.01	<0.01	2891341	384725	411640	16	WHMT	MEDU	THAL	Immune regulation	ALS ¹³

<i>JUN</i>	1	jun oncogene	ENSG00000177606	6204	1302	165160	rs2760496	0.01	<0.01	2415084	59246386	59268803	14	HIPP	FCTX	TCTX	Cell cycle	None reported
<i>KRT81</i>	12	keratin 81	ENSG00000205426	6458	3691	602153	rs3741722	<0.01	<0.01	3455261	52679699	52702146	6	FCTX	HIPP	TCTX	Keratin production	Neurodegeneration ¹⁴
<i>MAML1</i>	5	mastermind-like 1 (Drosophila)	ENSG00000161021	13632	5665	605424	rs12374446	0.01	<0.01	2844410	179159851	179219189	12	CRBL	WHMT	OCTX	Cell cycle	Alzheimer Disease, ¹⁵ Parkinson Disease, ¹⁵ ALS ¹⁵
<i>MDH1</i>	2	"malate dehydrogenase 1, NAD (soluble)"	ENSG00000014641	6970	1100	154200	rs1869700	<0.01	<0.01	2485176	63772665	63835619	14	OCTX	TCTX	FCTX	Cell proliferation and differentiation	Child-onset dystonia with optic atrophy and basal ganglia degeneration ¹⁶
<i>MECR</i>	1	mitochondrial trans-2-enoyl-CoA reductase	ENSG00000116353	19691	12192	608205	rs2068388	0.02	<0.01	2403793	29518582	29557444	16	FCTX	HIPP	TCTX	Mitochondrial metabolism	None reported
<i>MED15</i>	22	mediator complex subunit 15	ENSG00000099917	14248	12117	607372	rs12484992	0.01	<0.01	3937587	20847344	20941902	29	TCTX	FCTX	OCTX	Gene transcription	Neurodegeneration ¹⁷
<i>MPP3</i>	17	"membrane protein, palmitoylated 3 (MAGUK p55 subfamily member 3)"	ENSG00000161647	7221	3069	601114	rs8081646	0.03	0.01	3758640	41878177	41910537	23	CRBL	MEDU	HIPP	Cell membrane function	Alzheimer Disease, ¹⁸ Parkinson Disease ¹⁹
<i>MRPL30</i>	2	mitochondrial ribosomal protein L30	ENSG00000185414	14036	14751	611838	rs2632277	0.02	0.02	2495758	99755892	99768503	10	WHMT	CRBL	HIPP	Mitochondrial metabolism	Alzheimer Disease ²⁰
<i>MYBL2</i>	20	v-myb myeloblastosis viral oncogene homolog (avian)-like 2	ENSG00000101057	7548	3247	601415	rs619289	0.04	0.02	3886223	42294384	42345118	17	WHMT	THAL	SNIG	Cell cycle	None reported
<i>NBL1</i>	1	"neuroblastoma, suppression of tumorigenicity 1"	ENSG00000158747	7650	9001	600613	rs2854108	0.03	0.01	2323774	19751280	19985905	9	FCTX	TCTX	OCTX	Cell cycle	Huntington Disease ²¹
<i>NCOR1</i>	17	nuclear receptor co-repressor 1	ENSG00000141027	7672	2911	600849	rs3785631	0.04	0.04	3746881	15542407	16121039	52	CRBL	OCTX	TCTX	Gene transcription	ALS, ²² Neurodegeneration ²²
<i>NFIL3</i>	9	"nuclear factor, interleukin 3 regulated"	ENSG00000165030	7787	5619	605327	rs1591069	0.04	0.01	3214451	94171343	94187333	5	CRBL	OCTX	THAL	Immune regulation	Cerebellar degeneration ²³
<i>NFIX</i>	19	nuclear factor I/X (CCAAT-binding transcription factor)	ENSG00000008441	7788	1234	164005	rs8103241	<0.01	<0.01	3822122	13106604	13209605	23	WHMT	OCTX	CRBL	Gene transcription	Alzheimer Disease ²⁴
<i>NOTCH1</i>	9	"Notch homolog 1, translocation-associated (Drosophila)"	ENSG00000148400	7881	1827	190198	rs10116408	<0.01	<0.01	3230141	139388898	139440238	35	WHMT	MEDU	SNIG	Cytoskeletal function	Alzheimer Disease, ²⁵ Prion disease, Neurodegeneration
<i>NR5A1</i>	9	"nuclear receptor subfamily 5, group A, member 1"	ENSG00000136931	7983	1702	184757	rs7851142	0.03	0.01	3225058	127243515	127269699	11	SNIG	WHMT	PUTM	Gene transcription	Neurodegeneration ²⁶
<i>NR6A1</i>	9	"nuclear receptor subfamily 6, group A, member 1"	ENSG00000148200	7985	4147	602778	rs7851142	0.03	0.01	3225096	127279564	127534695	16	CRBL	TCTX	OCTX	Gene transcription, neurogenesis	Neurodegeneration ²⁷
<i>NUDCD3</i>	7	NudC domain containing 3	ENSG00000015676	22208	13831	610296	rs10280989	0.03	0.01	3048631	44421883	44530397	21	OCTX	FCTX	TCTX	Cytoskeletal function	Alzheimer Disease ²⁸
<i>PACS1</i>	11	phosphofurin acidic cluster sorting protein 1	ENSG00000175115	30032	6320	607492	rs2452681	0.01	<0.01	3335952	65837748	66012438	26	PUTM	HIPP	FCTX	Cellular trafficking	Neurodegeneration ²⁹

<i>PELP1</i>	17	"proline, glutamate and leucine rich protein 1"	ENSG00000141456	30134	10144	609455	rs4522461	0.01	<0.01	3742236	4574688	4607712	19	WHMT	FCTX	OCTX	Cell cycle and gene expression	None reported
<i>PIAS3</i>	1	"protein inhibitor of activated STAT, 3"	ENSG00000131788	16861	9068	605987	rs11577342	0.04	0.03	2432647	145585835	145621863	32	CRBL	PUTM	FCTX	Immune regulation	Alzheimer Disease, ³⁰ ALS ³⁰
<i>PKN2</i>	1	protein kinase N2	ENSG00000065243	9406	3972	602549	rs10489889	0.01	0.01	2345617	89101172	89301918	29	WHMT	CRBL	SNIG	Neuronal cytoskeletal organization	Parkinson Disease, ³¹ Alzheimer Disease ³²
<i>PLK2</i>	5	polo-like kinase 2 (Drosophila)	ENSG00000145632	19699	6118	607023	rs10071783	0.01	<0.01	2858023	57749815	57756867	15	PUTM	HIPP	TCTX	Cell division	None reported
<i>PPL</i>	16	periplakin	ENSG00000118898	9273	4187	602871	rs2075639	0.01	<0.01	3678462	4931712	4987140	23	OCTX	TCTX	FCTX	Keratin production	Alzheimer Disease, ³³ Frontotemporal dementia ³⁴
<i>PSEN1</i>	14	presenilin 1	ENSG00000080815	9508	87	104311	rs362398	0.03	0.01	3543481	73602818	73690398	23	WHMT	MEDU	SNIG	Chromosome organization and segregation	Frontotemporal dementia, ³⁵ Alzheimer Disease ³⁵
<i>PSMD11</i>	17	"proteasome (prosome, macropain) 26S subunit, non-ATPase, 11"	ENSG00000108671	9556	5119	604449	rs4794922	0.05	<0.01	3717737	30770974	30810336	17	TCTX	HIPP	FCTX	Proteasome function	Neurodegeneration, ³⁶ ALS ³⁶
<i>RAD23A</i>	19	RAD23 homolog A (S. cerevisiae)	ENSG00000179262	9812	7191	600061	rs1548546	<0.01	<0.01	3822074	13056654	13064768	11	FCTX	OCTX	TCTX	Proteasome function, DNA repair	None reported
<i>RALA</i>	7	v-ral simian leukemia viral oncogene homolog A (ras related)	ENSG00000006451	9839	1549	179550	rs17171603	<0.01	<0.01	2998404	39662526	39821761	12	MEDU	WHMT	SNIG	Mitochondrial metabolism	ALS, ³⁷ Frontotemporal dementia ³⁸
<i>RANGAP1</i>	22	Ran GTPase activating protein 1	ENSG00000100401	9854	3839	602362	rs1953	0.01	0.01	3961842	41639496	41698081	22	OCTX	TCTX	FCTX	Cell signaling	Hippocampal degeneration ³⁹
<i>RIT1</i>	1	Ras-like without CAAX 1	ENSG00000143622	10023	10195	609591	rs822503	0.03	0.01	2437736	155869377	155881167	8	SNIG	MEDU	PUTM	Cell survival	ALS, Alzheimer Disease ⁴⁰
<i>SATB1</i>	3	SATB homeobox 1	ENSG00000182568	10541	3647	602075	rs17519462	0.02	<0.01	2665199	18389431	18487082	23	OCTX	FCTX	TCTX	Gene expression	None reported
<i>SEC62</i>	3	SEC62 homolog (S. cerevisiae)	ENSG00000008952	11846	3706	602173	rs2072576	<0.01	<0.01	2651782	169683752	169711959	14	CRBL	WHMT	TCTX	Gene expression	None reported
<i>SKIL</i>	3	SKI-like oncogene	ENSG00000136603	10897	1319	165340	rs4955588	<0.01	<0.01	2651989	170075513	170111436	13	TCTX	FCTX	SNIG	Cell proliferation and differentiation	Alzheimer Disease ⁴¹
<i>SLC2A4</i>	17	"solute carrier family 2 (facilitated glucose transporter), member 4"	ENSG00000181856	11009	688	138190	rs222852	<0.01	<0.01	3708399	7184977	7191556	15	SNIG	PUTM	THAL	Cell proliferation and differentiation	Frontotemporal dementia ⁴²
<i>SMAD3</i>	15	SMAD family member 3	ENSG00000166949	6769	4380	603109	rs16950615	0.04	<0.01	3598959	67357989	67509764	20	PUTM	FCTX	TCTX	Cell proliferation and differentiation	Frontotemporal dementia ⁴²
<i>SMAD4</i>	18	SMAD family member 4	ENSG00000141646	6770	2995	600993	rs2202980	0.02	0.01	3788302	48554802	48607297	19	CRBL	HIPP	PUTM	Cell proliferation and differentiation	None reported
<i>SS18</i>	18	"synovial sarcoma translocation, chromosome 18"	ENSG00000141380	11340	2559	600192	rs4800708	<0.01	<0.01	3802129	23450259	23671399	19	WHMT	MEDU	SNIG	Transcription initiation and regulation	Alzheimer Disease ⁴³

<i>STAT6</i>	12	"signal transducer and activator of transcription 6, interleukin-4 induced"	ENSG00000166888	11368	3302	601512	rs17119386	0.01	0.01	3458337	57488868	57516709	25	FCTX	TCTX	PUTM	Immune regulation	None reported
<i>SUB1</i>	5	SUB1 homolog (S. cerevisiae)	ENSG00000113387	19985	2737	600503	rs648658	0.03	<0.01	2805581	32522864	32627015	5	FCTX	TCTX	HIPP	Transcription initiation and regulation	None reported
<i>TAL1</i>	1	T-cell acute lymphocytic leukemia 1	ENSG00000162367	11556	1753	187040	rs2070929	0.02	0.01	2411198	47681966	47698294	14	SNIG	THAL	WHMT	Immune regulation	None reported
<i>TEF</i>	22	thyrotrophic embryonic factor	ENSG00000167074	11722	1783	188595	rs2073167	0.01	<0.01	3946817	41763482	41795325	15	CRBL	PUTM	OCTX	Transcription initiation and regulation	None reported
<i>TFDP1</i>	13	transcription factor Dp-1	ENSG00000198176	11749	1792	189902	rs12020712	0.01	<0.01	3502710	114238807	114302563	12	CRBL	WHMT	MEDU	Cell cycle	None reported
<i>TH1L</i>	20	TH1-like (Drosophila)	ENSG00000101158	15934	16096	605297	rs4812048	0.01	<0.01	3891278	57555821	57571779	26	WHMT	CRBL	MEDU	Transcription initiation and regulation	None reported
<i>THADA</i>	2	thyroid adenoma associated	ENSG00000115970	19217	18177	611800	rs7589033	0.01	<0.01	2550542	43457634	43823177	46	WHMT	PUTM	SNIG	Apoptosis	None reported
<i>THSD7A</i>	7	"thrombospondin, type I, domain containing 7A"	ENSG00000005108	22207		612249	rs83	0.03	<0.01	3038664	11251133	11901972	31	THAL	OCTX	TCTX	Cell migration	Prion disease ⁴⁴
<i>TRIM41</i>	5	tripartite motif-containing 41	ENSG00000146063	19013	15558	610530	rs254460	<0.01	0.01	2845043	180649519	180662790	18	WHMT	MEDU	THAL	Protein modification	None reported
<i>UBE2I</i>	16	"ubiquitin-conjugating enzyme E2I (UBC9 homolog, yeast)"	ENSG00000103275	12485	9045	601661	rs6600128	<0.01	<0.01	3643703	1349450	1377015	19	CRBL	HIPP	FCTX	Cell signaling	Alzheimer Disease ⁷
<i>YY1</i>	14	YY1 transcription factor	ENSG00000100811	12856	2482	600013	rs3825555	0.04	0.03	3551677	100680630	100749115	14	FCTX	TCTX	OCTX	Immune regulation	None reported
<i>ZNF622</i>	5	zinc finger protein 622	ENSG00000173545	30958	12278	608694	rs4702146	0.01	<0.01	2849960	16409108	16466047	8	SNIG	TCTX	THAL	Transcription initiation and regulation	Cerebellar degeneration ⁴⁵

Supplemental Table S3 Legend. Additional results summarizing and annotating the VEGAS and PINBPA results are shown. For each gene, we provide the full name and alternate identifiers along with VEGAS summary statistics, the top 3 regions expressing each gene in healthy human tissue, OMIM biological process implicated for each gene, and known neurodegenerative disease associations are shown. In order to analyze the location and expression patterns of the svPPA network in healthy human tissue, we used the Braineac Database (www.braineac.org) from the UK Brain Expression Consortium (UKBEC). The dataset contains mRNA quantification data from 134 brains from neuropathologically confirmed healthy individuals from the MRC Sudden Death Brain Bank in Edinburgh, UK, and the Sun Health Research Institute in Sun City West, USA. Ten

regions of the brain were available for analysis: occipital cortex, frontal cortex, temporal cortex, hippocampus, intralobular white matter, cerebellar cortex, thalamus, putamen, substantia nigra, and medulla. RNA expression quantification was assessed using the Affymetrix Exon 1.0 ST Array following the manufacturer's protocols. For full details on RNA extraction, QC processes, and information regarding analysis of array data see (www.braineac.org). Braineac combines probe sets to create a gene expression profile for each gene using a Winsorized mean across the available probe-sets. We retrieved the expression data for each of the 64 genes in the svPPA network. When multiple expression profiles were available for a given gene, we chose the profile with the largest number of probes for inclusion in our analyses. Chr # – chromosomal number, ENSEMBL ID – annotation ID in ENSEMBL, HGNC ID – Human genome nomenclature ID, HPRD ID – Human protein reference database, MIMID – Mendelian inheritance in man ID, P-value – Gene p value, Top SNP p-value – Top p value for SNP, Braineac ID – Braineac reference database, Start location– Start of chromosomal sequence location, Stop location– End of chromosomal sequence location, Region ranks 1-3 – Top three brain regions where gene is expressed, CB – Cerebellar Cortex, FL – Frontal lobe cortex, HIP – Hippocampus, MED – Medulla, OL – Occipital lobe cortex, PUT – Putamen, SN – Substantia Nigra, TL – Temporal lobe cortex, OMIM Biological Process –Online Mendelian Inheritance in Man biological process reported for each gene.

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Supplementary Table S4: Reactome gene ontology pathways for semantic dementia

Reactome pathways	Reference list	# Genes overlapping	# Genes expected	Fold Enrichment	P-value
Signaling by Activin (R-HSA-1502540)	13	3	0.04	74.46	1.79E-02
Pre-NOTCH Transcription and Translation (R-HSA-1912408)	29	6	0.09	66.75	9.56E-07
Downregulation of SMAD2/3:SMAD4 transcriptional activity (R-HSA-2173795)	23	4	0.07	56.11	1.65E-03
Pre-NOTCH Expression and Processing (R-HSA-1912422)	45	6	0.14	43.02	1.28E-05
Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors (R-HSA-8864260)	34	4	0.11	37.96	7.67E-03
Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer (R-HSA-2173793)	44	5	0.14	36.66	5.37E-04
NOTCH1 Intracellular Domain Regulates Transcription (R-HSA-2122947)	45	4	0.14	28.68	2.29E-02
Signaling by TGF-beta Receptor Complex (R-HSA-170834)	72	5	0.22	22.41	5.89E-03
Signaling by NOTCH (R-HSA-157118)	108	7	0.33	20.91	9.14E-05
Nucleotide Excision Repair (R-HSA-5696398)	110	5	0.34	14.67	4.48E-02
Diseases of signal transduction (R-HSA-5663202)	282	8	0.87	9.15	4.84E-03
Generic Transcription Pathway (R-HSA-212436)	834	17	2.58	6.58	8.26E-07
Developmental Biology (R-HSA-1266738)	806	12	2.5	4.8	1.11E-02
Disease (R-HSA-1643685)	899	12	2.79	4.31	3.29E-02
Gene Expression (R-HSA-74160)	1693	21	5.25	4	3.58E-05
Unclassified (UNCLASSIFIED)	11676	21	36.19	0.58	0.00E+00

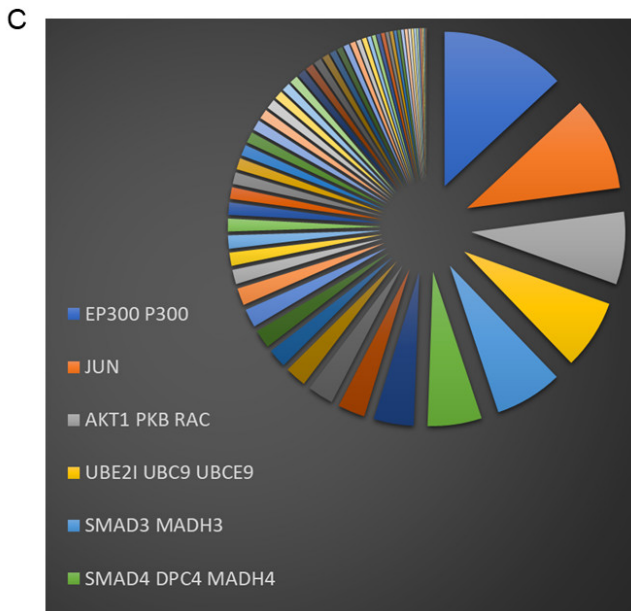
Supplementary Table S4 Legend. Reactome pathways highlighted in our ontological analysis and corresponding pathway reference numbers. Reference list – number of genes documented

in the Reactome database for each pathway, # Genes overlapping – number of genes in both pathway reference list and set of enriched svPPA genes, # Genes expected – Reactome a priori expected degree of overlap given number of genes entered into the pathway analysis tool, Fold enrichment – Reactome degree of enrichment based on expected value and number of overlapping genes, p value – Bonferroni corrected p values.

SUPPLEMENTAL FIGURES

Supplementary Figure 1. Interactome Results

A Top 10 interactomes by dimension		B Contribution to the network	
Seed	# direct interactors	# Seeds	percentage contribution
EP300	311	1	>10 %
JUN	234	1	>8 %
AKT1	181	3	>7 %
UBE2I	174	2	>4 %
SMAD3	169	3	>2 %
SMAD4	135	17	>1 %
NCOR1	100	11	>0.5 %
HNF4A	68	25	>0.1 %
YY1	65		
PSMD11	53		



Supplemental Figure 1 Legend. Detailed interactome analysis results are shown. (A) The top 10 interactomes ranked by number of interactors. (B) Percentage contribution to the network for each seed in the analysis is shown. (C) Graphical depiction of the results shown in (A).

Supplemental Figure 2. Comparison of svPPA network against randomly sampled networks

Dataset	Number of seeds	Subnetwork nodes around seeds	Number of edges	Average number of neighbors	Network density
random 1	7	14	8	1.143	0.088
random 2	7	29	30	1.793	0.064
random 3	7	17	11	1.294	0.081
random 4	7	47	46	1.957	0.043
random 5	7	16	11	1.375	0.092
random 6	70	145	172	2.193	0.015
random 7	70	133	146	2.165	0.016
random 8	70	142	150	2.014	0.014
random 9	70	195	223	2.133	0.011
random 10	70	149	146	1.933	0.013
SD-FTD IIHs	7	37	93	4.703	0.131

Supplemental Figure 2 Legend. Results for the comparison of svPPA (SD-FTD) network against randomly sampled parts of the network.

IFGC APPENDICES

APPENDIX A

Acknowledgments

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