

Supplemental Table 3. PPM2 patients who carry a potentially deleterious phenocopy variant

Clinical characteristics													Genetic Variants					Genotyping Method		Variant annotations (Ingenuity Variant Analysis)																										
Cohort	ID	Sex	Age at onset	Family history of MS	Progression since onset	Elevated IgG index	Oligoclonal bands	Positive CSF (p0 index or OCs)	Brain MRI	Spinal cord MRI	Cocclusion enhancement	Meigs 2018 Criteria PPM2	Gene	Variant Type	Transcript Variant	Protein Variant	Phenocopy Disorder	Inheritance	Reported in literature	WGS	MS replication chip	OpenKary	Genomic position	Ref allele	Alt allele	CADD Score	MAF ExAC European	Inferred Functional Activity	Translation Impact	Classification by Ingenuity Variant Analysis	SIFT Function Prediction	SIFT Score	PolyPhen-2 Function Prediction	Conservation phyloP p-value	Regulatory Site	APC Frequency	APC European Frequency	1000 Genomes Frequency	NHLBI ESP European Frequency	ExAC Frequency All populations	ExAC European Frequency	gnp				
Discovery	650368	F	37	-	-	ND	ND	ND	+	+	-	Yes	SPF5A	Missense	c.238C>T	p.A231V	SPD10	AD	+	ND	ND	+	11,970,413	C	T	23.1	0.02%	loss	missense	Uncertain Significance	Tolerated	0.3	Benign	1.15E-05	-	0.03	0.03	0.02	-	0.03	0.03	0.02	0.03	0.03	12,394,041 C>T	
Discovery	041223	F	51	-	-	+	+	+	+	-	-	Yes	MLC1	Missense	c.274C>T	p.P253	MLC	AR	+	ND	ND	+	22,502,182	G	A	26.8	0.04%	loss	missense	Uncertain Significance	-	-	4.25E-05	-	0.011	0.004	-	-	0.011	0.004	-	0.011	0.004	22,501,820 C>T		
Discovery	650362	F	47	-	-	+	+	+	+	-	-	Yes	SCZ3	Missense	c.223A>G	p.E75K	TS	AD	+	ND	ND	+	12,912,045	G	A	24.9	0.01%	normal	missense	Uncertain Significance	Damaging	0.02	Benign	3.12E-08	-	0.032	0.02	-	0.032	0.02	-	0.032	0.02	16,130,465 G>A		
Discovery	650008	F	50	-	-	+	+	+	+	-	-	Yes	REEP1	Splicing site	c.606-430>T	-	SPD31	AD	+	ND	ND	+	2,864,480	C	A	16.22	0.11%	normal	synonymous	Likely Benign	-	-	-	-	0.073	0.116	-	-	0.073	0.116	-	0.073	0.116	2,864,418 G>A		
Discovery	650319	F	25	+	-	+	+	+	+	+	-	Yes	SPD11	Missense	c.628C>T	p.R209C	SPD11	AR	+	ND	ND	+	15,448,971	G	A	35	0.04%	loss	missense	Uncertain Significance	Damaging	0	Probably Damaging	3.88E-07	-	0.03	0.043	-	-	0.03	0.043	-	0.03	0.043	15,448,971 G>A	
Discovery	000200	F	28	-	-	+	+	+	+	ND	-	Yes	KIAA1248	Missense	c.253A>C	p.H82Y	SPD8	AD	+	ND	ND	+	8,126,589	G	A	19.53	0.00%	normal	missense	Uncertain Significance	Tolerated	0.74	Benign	4.19E-05	-	0.003	0	-	0.003	0	-	0.003	0	8,126,589 G>A		
Discovery	041807	F	36	-	-	+	+	+	+	+	-	Yes	RTN6	Missense	c.620G>T	p.H76L	SGP12	AD	+	ND	ND	+	19,408,110	C	A	27	0.00%	normal	missense	Uncertain Significance	-	-	Benign	3.15E-03	-	0.001	0	-	0	0	-	0	0.001	0	19,408,110 C>A	
Discovery	650053	M	36	-	-	+	+	+	+	+	-	Yes	SPFA7	Splice Site	c.1350+10>A	-	SPG4	AD	+	ND	ND	+	2,328,465	G	A	27.7	0.00%	loss	-	-	Putogenic	-	-	8.86E-06	-	-	-	-	-	-	-	-	-	2,328,465 G>A		
Discovery	041282	F	46	-	-	+	+	+	+	+	-	Yes	SPD11	Missense	c.673C>T	p.L231F	SPD11	AR	+	ND	ND	+	15,448,982	G	A	25	0.17%	normal	missense	Uncertain Significance	Tolerated	0.06	Possibly Damaging	1.12E-03	-	0.15	0.178	0.18	0.221	0.131	0.173	15,448,982 G>A				
Discovery	041548	M	27	-	-	+	+	+	+	+	-	Yes	SPD21	Missense	c.2230A>A	p.A71T	SPD21	AR	+	ND	ND	+	15,892,720	C	T	33	0.00%	normal	missense	Uncertain Significance	Damaging	0.05	Benign	1.85E-04	-	0.003	0.002	-	-	0.003	0.002	-	-	0.003	0.002	15,892,720 C>T
Discovery	150047	M	28	-	-	ND	ND	+	+	+	-	Yes	AP2M1	Missense	c.1140G>A	p.M36I	SPD30	AR	+	ND	ND	+	7,787,043	G	A	20.4	0.01%	normal	missense	Uncertain Significance	Tolerated	0.43	Benign	4.97E-05	-	0.05	0.028	0.04	0.04	0.04	0.04	0.04	7,787,043 G>A			
Discovery	650084	F	48	-	-	+	+	+	+	+	-	Yes	SPD7	Splice Site	c.135+10>T	-	SPD7	AR	+	ND	ND	+	16,896,319	G	T	23.9	0.00%	loss	-	-	Likely Pathogenic	-	-	8.91E-07	-	0.004	0.006	0.06	0.03	0.003	0.005	0.003	0.005	16,896,319 G>T		
Discovery	041807	F	36	-	-	+	+	+	+	+	-	Yes	CPYBP2	Missense	c.1057G>C	p.R354L	SPD20	AR	+	ND	ND	+	4,108,640	T	C	23.2	0.00%	normal	missense	Uncertain Significance	Tolerated	0.11	Possibly Damaging	1.56E-05	-	0.12	0.21	0.16	0.14	0.187	0.226	0.14	0.187	4,108,640 T>C		
Discovery	041181	M	44	+	-	-	-	+	+	+	-	Yes	AP14B	Missense	c.1100G>A	p.R367G	SPD20	AR	+	ND	ND	+	7,997,100	G	A	34	0.04%	normal	missense	Uncertain Significance	Tolerated	0.11	Possibly Damaging	1.56E-05	-	0.005	0.04	0.02	0.028	0.02	0.028	0.04	0.02	0.028	7,997,100 G>A	
Discovery	041181	M	44	+	-	-	-	+	+	+	-	Yes	KIAA1248	Missense	c.847C>T	p.P216L	SPD8	AD	+	ND	ND	+	8,126,591	G	A	25.9	0.19%	normal	missense	Uncertain Significance	Tolerated	0.08	Possibly Damaging	3.61E-06	-	0.14	0.183	0.02	0.209	0.122	0.194	0.209	0.122	0.194	8,126,591 G>A	
Discovery	041181	M	44	+	-	-	-	+	+	+	-	Yes	IGBP4	Missense	c.1191G>C	p.R397P	SPD4	AR	+	ND	ND	+	19,201,020	C	G	12.35	0.18%	gain	missense	Uncertain Significance	Adaptive	1	Benign	3.91E-03	-	0.129	0.19	-	-	0.129	0.19	-	-	0.129	0.19	19,201,020 C>G
Discovery	600129	M	41	-	-	ND	ND	ND	+	+	-	Yes	SPD11	Missense	c.673C>T	p.L231F	SPD11	AR	+	ND	ND	+	15,448,982	G	A	25	0.17%	normal	missense	Uncertain Significance	Tolerated	0.06	Possibly Damaging	1.12E-03	-	0.14	0.177	0.18	0.221	0.131	0.173	15,448,982 G>A				
Discovery	600129	M	41	-	-	ND	ND	ND	+	+	-	Yes	KP1A	Missense	c.337C>T	p.P118L	SPD20	AR	+	ND	ND	+	22,918,075	G	A	31.2	0.04%	normal	missense	Uncertain Significance	Tolerated	0.51	Benign	1.35E-03	-	0.039	0.035	0.05	0.02	0.012	0.052	0.048	0.012	0.052	22,918,075 G>A	
Discovery	510039	F	34	-	-	-	-	+	+	+	-	Yes	KP2A	Missense	c.388C>T	p.P122L	SPD10	AD	+	ND	ND	+	12,570,802	G	C	19.07	0.03%	normal	missense	Uncertain Significance	Tolerated	0.5	Benign	2.15E-03	-	0.037	0.039	0.04	0.07	0.038	0.036	0.07	0.038	0.036	12,570,802 G>C	
Discovery	600382	M	54	-	-	ND	ND	ND	+	+	-	Yes	SD47	Missense	c.483A>C	p.L228L	CPD1	AR	+	ND	ND	+	2,171,005	A	C	11.77	0.07%	normal	missense	Uncertain Significance	Tolerated	0.71	Benign	3.79E-04	-	0.026	0.042	0.04	0.047	0.026	0.037	0.04	0.047	0.026	0.037	2,171,005 A>C
Discovery	040007	M	48	-	-	+	-	+	+	+	-	Yes	KP1A	Missense	c.428C>T	p.A148V	SPD20	AR	+	ND	ND	+	22,918,194	G	A	16.56	0.461%	normal	missense	Uncertain Significance	Tolerated	0.11	Benign	6.00E-04	-	0.345	0.631	0.08	0.516	0.244	0.461	0.516	0.244	0.461	22,918,194 G>A	
Discovery	650142	M	51	-	-	ND	ND	ND	+	+	-	Yes	AP2D1	Missense	c.228T>G	p.V763M	SPD48	AR	+	ND	ND	+	7,482,879	G	A	29.5	0.00%	loss	missense	Uncertain Significance	Damaging	0	Probably Damaging	1.75E-04	-	0.015	0.01	0.02	0.005	0.005	0.01	0.009	0.005	0.01	0.009	7,482,879 G>A
Discovery	700019	F	61	-	-	+	+	+	+	+	-	Yes	SPD7	Missense	c.1150G>C	p.G364I	SPD7	AD	+	ND	ND	+	16,896,134	C	T	32	0.371%	normal	missense	Uncertain Significance	Damaging	0	Probably Damaging	8.91E-07	-	0.295	0.416	0.22	0.463	0.252	0.371	0.252	0.371	16,896,134 C>T		
Discovery	150057	F	37	-	-	+	+	+	+	+	-	Yes	PNPLA8	Missense	c.145T>C	p.R49L	SPD39	AR	+	ND	ND	+	19,782,741	C	T	22.8	0.83%	normal	missense	Uncertain Significance	Tolerated	0.39	Benign	1.19E-04	-	0.522	0.841	0.359	0.687	0.548	0.839	0.687	0.548	19,782,741 C>T		
Discovery	510014	M	64	-	-	+	+	+	+	ND	-	Yes	YFSD7A	Missense	c.625C>A	p.L20H	SPD3	AR	+	ND	ND	+	8,171,393	C	A	34	0.06%	loss	missense	Uncertain Significance	Damaging	0.05	Possibly Damaging	2.31E-05	-	0.036	0.041	-	-	0.036	0.041	-	-	0.036	0.041	8,171,393 C>A
Discovery	510051	M	44	-	-	+	+	+	+	-	-	Yes	JAK2B	Missense	c.574T>C	p.R191	SPD2	AR	+	ND	ND	+	6,413,094	T	C	21.9	0.11%	normal	missense	Uncertain Significance	Tolerated	0.5	Possibly Damaging	4.15E-05	-	0.081	0.087	-	-	0.081	0.087	-	-	0.081	0.087	6,413,094 T>C
Discovery	650095	M	34	-	-	ND	ND	+	+	-	-	Yes	ZFYVE28	Missense	c.295C>T	p.T293I	SPD15	AR	+	ND	ND	+	14,892,051	G	A	23.8	0.37%	loss	missense	Uncertain Significance	Damaging	0.51	Possibly Damaging	8.86E-04	-	0.247	0.357	0.18	0.38	0.255	0.372	0.18	0.38	0.255	0.372	14,892,051 G>A
Replication	500189	F	29	-	-	Not available	Not available	+	+	+	-	Not enough data	REEP1	Splicing site	c.606-430>T	-	SPD31	AD	+	ND	ND	+	2,864,480	C	A	16.22	0.11%	normal	synonymous	Likely Benign	-	-	-	-	0.073	0.116	-	-	0.073	0.116	-	-	0.073	0.116	2,864,418 G>A	
Replication	500189	M	57	-	-	ND	ND	ND	+	ND	-	Not enough data	REEP1	Splicing site	c.606-430>T	-	SPD31	AD	+	ND	ND	+	2,864,480	C	A	16.22	0.11%	normal	synonymous	Likely Benign	-	-	-	-	0.073	0.116	-	-	0.073	0.116	-	-	0.073	0.116	2,864,418 G>A	

ND = not done