

Supplemental Table S1. Characteristics of the Total MEN1 Cohort 117 Patients

No.	Sex	Age, yr	Family history	Variant	Protein	Variant classification	Parathyroid tumor	Pancreas tumor	Pituitary tumor	Thymic tumor	Adrenal tumor	Other malignancies	Reference
1	F	54	+	c.69del	p.Phe23Leufs*96	PV	+	-	-	-	-	EM polyp	[1]
2	F	25	+	c.89_90del	p.Glu30Glyfs*86	PV	+	-	+	-	-	-	[2]
3	F	43	-	c.122T>G	p.Leu41Arg	LPV	+	+	-	-	-	BC	Novel
4	F	48	-	c.133G>A	p.Glu45Lys	LPV	-	-	+	-	+	-	[3]
5	F	42	-	c.176_179dup	p.Glu60Aspfs*58	LPV	+	-	+	-	-	-	Novel
6	M	57	-	c.196_200dup	p.Asp70Profs*51	PV	+	+	-	-	-	HCC	[4]
7	M	47	+	c.196_200dup	p.Asp70Profs*51	PV	+	+	-	-	-	-	[4]
8	F	38	-	c.196_200dup	p.Asp70Profs*51	PV	+	+	+	-	-	-	[4]
9	F	54	-	c.196_200dup	p.Asp70Profs*51	PV	+	+	-	-	+	-	[4]
10	M	52	-	c.225_226insT	p.Thr76Tyrfs*41	PV	+	+	+	-	+	-	[5]
11	F	28	+	c.235_252del	p.Pro79_Ser84del	VUS	-	+	-	-	-	-	Novel
12	M	32	+	c.235_252del	p.Pro79_Ser84del	VUS	-	+	-	-	-	-	Novel
13	F	18	-	c.245del	p.Asp82Alafs*37	PV	-	+	+	-	-	BC	Novel
14	F	42	+	c.275_286del	p.Arg92_Arg95del	LPV	+	+	-	-	-	-	[6]
15	F	64	-	c.322C>T	p.Arg108*	PV	+	+	+	-	-	-	[7]
16	M	47	-	c.326_341del	p.Glu109Alafs*5	PV	+	+	-	-	-	-	Novel
17	M	43	-	c.358_360del	p.Asn120del	PV	+	+	+	-	+	-	[8]
18	F	28	+	c.378G>A	p.Trp126*	PV	+	-	+	-	-	-	[9]
19	F	31	+	c.378G>A	p.Trp126*	PV	+	+	+	-	-	-	[9]
20	F	52	-	c.378G>A	p.Trp126*	PV	+	+	+	-	+	-	[9]
21	F	35	+	c.383_398del	p.Ser128Thrfs*52	PV	-	-	+	-	-	Myoma	[5]
22	M	28	+	c.383_398del	p.Ser128Thrfs*52	PV	-	-	+	-	-	-	[5]
23	F	29	+	c.383_398del	p.Ser128Thrfs*52	PV	+	-	+	-	-	-	[5]
24	F	43	-	c.442A>C	p.Thr148Pro	LPV	+	+	+	-	-	-	[10]
25	F	43	-	c.442A>C	p.Thr148Pro	LPV	+	+	+	-	-	-	[10]
26	M	47	-	c.452_453del	p.Lys151Ilefs*28	LPV	+	+	-	-	-	-	Novel
27	F	41	-	c.484G>T	p.Val162Phe	VUS	+	-	+	-	-	-	[1]
28	M	54	+	c.514del	p.Asp172Metfs*13	PV	+	+	+	-	-	Meningioma	Novel
29	M	26	-	c.548G>A	p.Trp183*	PV	+	-	+	-	-	-	[11]
30	F	63	-	c.558del	p.Phe186Leufs*38	PV	+	+	+	-	-	-	[12]
31	F	9	+	c.628_631del	p.Thr210Serfs*13	PV	-	-	-	-	-	-	[8]
32	F	43	-	c.628_631del	p.Thr210Serfs*13	PV	+	+	+	-	-	-	[8]

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No.	Sex	Age, yr	Family history	Variant	Protein	Variant classification	Parathyroid tumor	Pancreas tumor	Pituitary tumor	Thyroid tumor	Adrenal tumor	Other malignancies	Reference
33	M	37	+	c.643G>A	p.Val215Met	LPV	-	+	-	-	-		[3]
34	M	68	-	c.643G>A	p.Val215Met	LPV	+	+	-	+	+		[3]
35	M	79	-	c.654+2T>C	p.?	LPV	+	+	-	-	-		Novel
36	F	73	+	c.660G>C	p.Trp220Cys	LPV	+	+	+	-	-		Novel
37	F	21	+	c.681del	p.Tyr227*	PV	+	+	+	-	-		Novel
38	M	23	-	c.694C>T	p.Arg232Cys	VUS	+	-	-	-	-	Osteosarcoma	[13]
39	M	60	-	c.722dup	p.Cys241Trpfs*8	PV	+	+	-	+	-		Novel
40	F	5	+	c.722dup	p.Cys241Trpfs*8	PV	-	-	-	-	-		Novel
41	F	39	+	c.722dup	p.Cys241Trpfs*8	PV	+	+	-	-	-		Novel
42	F	40	-	c.722dup	p.Cys241Trpfs*8	PV	+	+	-	-	-		Novel
43	M	70	-	c.722dup	p.Cys241Trpfs*8	PV	+	+	-	-	-		Novel
44	F	26	-	c.722G>A	p.Cys241Tyr	PV	+	+	-	-	-		[14]
45	F	60	-	c.758C>T	p.Ser253Leu	PV	+	-	-	-	-		[15]
46	M	27	-	c.772C>T	p.Gln258*	PV	+	+	-	-	-		[16]
47	F	26	+	c.784-9G>A	p.?	PV	+	+	+	-	-		[17]
48	F	30	+	c.784-9G>A	p.?	PV	+	+	+	-	-		[17]
49	F	29	-	c.818T>C	p.Leu273Pro	LPV	+	+	+	-	-		[18]
50	M	70	+	c.824G>A	p.Arg275Lys	PV	+	+	-	-	+		[19]
51	M	57	-	c.825-2A>G	p.?	PV	+	+	+	-	-		[20]
52	F	16	+	c.825-2A>G	p.?	PV	-	+	-	-	-		[20]
53	F	42	+	c.825-2A>G	p.?	PV	+	+	+	-	-		[20]
54	F	61	+	c.825-2A>G	p.?	PV	+	+	+	-	-		[20]
55	M	44	+	c.825-2A>G	p.?	PV	+	+	-	-	-		[20]
56	F	34	-	c.830C>T	p.Pro277Leu	PV	+	+	+	-	-		[21]
57	F	64	+	c.878del	p.Pro293Leufs*75	PV	+	+	-	-	-		[22]
58	F	62	+	c.878del	p.Pro293Leufs*75	PV	+	-	-	-	-		[22]
59	M	45	-	c.938_942del	p.Tyr313*	PV	+	+	+	-	-		Novel
60	F	41	+	c.938_942del	p.Tyr313*	PV	+	+	-	-	-	Ovary cystadenoma	Novel
61	F	41	+	c.973G>C	p.Ala325Pro	LPV	+	+	+	-	-		[23]
62	F	54	-	c.1031C>G	p.Thr344Arg	PV	+	+	+	-	-		[24]
63	F	47	-	c.1049+2T>G	p.?	PV	+	+	+	-	-		[25]
64	F	32	+	c.1049A>T	p.Asp350Val	LPV	-	-	-	-	-		[26]

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No.	Sex	Age, yr	Family history	Variant	Protein	Variant classification	Parathyroid tumor	Pancreas tumor	Pituitary tumor	Thyroid tumor	Adrenal tumor	Other malignancies	Reference
65	F	54	+	c.1049A>T	p.Asp350Val	LPV	+	+	+	-	-		[26]
66	M	32	+	c.1049A>T	p.Asp350Val	LPV	+	-	-	-	-		[26]
67	M	61	-	c.1049A>T	p.Asp350Val	LPV	+	+	-	-	-		[26]
68	F	17	+	c.1121_1126delinsGGGGA	p.Asn374Argfs*3	PV	-	+	+	-	-		[27]
69	F	20	+	c.1121_1126delinsGGGGA	p.Asn374Argfs*3	PV	-	+	+	-	+		[27]
70	M	50	+	c.1121_1126delinsGGGGA	p.Asn374Argfs*3	PV	+	+	+	-	+		[27]
71	F	62	+	c.1213C>T	p.Gln405*	PV	+	+	+	+	-		[23]
72	F	40	+	c.1213C>T	p.Gln405*	PV	+	-	+	-	-		[23]
73	M	20	-	c.1243C>T	p.Arg415*	PV	+	+	-	-	-		[7]
74	F	38	-	c.1253A>G	p.Asp418Gly	LPV	+	+	-	-	-		Novel
75	M	54	-	c.1253A>G	p.Asp418Gly	LPV	+	+	-	-	+		Novel
76	M	43	+	c.1324C>T	p.Gln442*	PV	+	+	+	+	-		[28]
77	F	65	+	c.1324C>T	p.Gln442*	PV	-	+	-	-	-		[28]
78	F	55	+	c.1324C>T	p.Gln442*	PV	+	+	+	-	-	Leiomyoma	[28]
79	M	26	+	c.1324C>T	p.Gln442*	PV	+	+	+	-	-		[28]
80	F	54	-	c.1350+1G>T	p.?	LPV	+	+	-	-	-		Novel
81	M	32	-	c.1351+2A>G	p.?	PV	+	-	+	-	-		[29]
82	F	64	+	c.1378C>T	p.Arg460*	PV	+	+	+	-	-		[24]
83	M	66	-	c.1378C>T	p.Arg460*	PV	+	+	+	-	-		[24]
84	F	32	-	c.1382_1389dup	p.Ala464Argfs*98	PV	+	+	+	-	-		[30]
85	M	59	-	c.1382_1389dup	p.Ala464Argfs*98	PV	+	+	-	-	+		[30]
86	F	46	-	c.1390del	p.Ala464Argfs*95	PV	+	+	+	-	-		Novel
87	M	38	-	c.1471G>T	p.Gln473*	PV	+	+	-	-	-		[31]
88	M	62	+	c.1522C>T	p.Gln508*	PV	+	-	+	+	-	HCC	[32]
89	F	48	+	c.1522C>T	p.Gln508*	PV	+	+	+	-	-		[32]
90	M	56	-	c.1522C>T	p.Gln508*	PV	+	+	+	-	+		[32]
91	M	38	-	c.1546dup	p.Arg516Profs*15	PV	+	+	-	-	-		[24]
92	M	79	+	c.1548dup	p.Lys517Glufs*14	PV	+	+	-	-	-	ZES	[33]
93	M	50	+	c.1650dup	p.Leu551Alafs*6	PV	+	+	-	-	-		Novel
94	F	57	-	c.1663A>T	p.Ser555Cys	LPV	-	+	-	-	-		[34]
95	F	54	+	c.1663A>T	p.Ser555Cys	LPV	+	-	-	-	-		[34]
96	M	58	+	c.1663A>T	p.Ser555Cys	LPV	-	-	-	-	+		[34]

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Supplemental Table S1. Continued

No.	Sex	Age, yr	Family history	Variant	Protein	Variant classification	Parathyroid tumor	Pancreas tumor	Pituitary tumor	Thymic tumor	Adrenal tumor	Other malignancies	Reference
97	M	61	+	c.1663A>T	p.Ser555Cys	LPV	+	+	-	-	-		[34]
98	F	56	-	c.1665T>A	p.Ser555Arg	LPV	+	+	-	-	-		Novel
99	F	64	+	c.1668del	p.Lys557Argfs*2	PV	+	+	+	-	-		Novel
100	M	33	+	c.1668del	p.Lys557Argfs*2	PV	+	-	-	-	-		Novel
101	F	50	-	Exon 1-10 deletion		PV	+	+	+	-	-	BC	[35]
102	M	68	+	No variant			+	+	+	+	-	HCC, ZES	
103	F	51	+	No variant			+	+	+	-	+	BC, EM polyp, myoma	
104	F	42	+	No variant			+	+	-	-	-		
105	F	40	-	No variant			+	-	+	-	-		
106	F	39	-	No variant			-	+	+	-	-		
107	F	48	-	No variant			+	+	+	-	-		
108	F	50	-	No variant			+	+	+	-	-		
109	F	64	-	No variant			+	+	+	-	-		
110	F	70	-	No variant			+	+	+	-	+		
111	F	76	-	No variant			-	+	+	-	-		
112	M	36	-	No variant			+	-	+	-	-		
113	M	41	-	No variant			+	+	+	+	-		
114	M	44	-	No variant			+	-	-	+	-		
115	M	45	-	No variant			+	+	-	+	-		
116	M	46	-	No variant			+	+	+	-	-		
117	M	63	+	No variant			+	+	+	-	+		

MEN1, multiple endocrine neoplasia type 1; *, termination codon; PV, pathogenic variant; EM, endometrial; LPV, likely pathogenic variant; BC, breast cancer; HCC, hepatocellular carcinoma; VUS, variant of uncertain significance; ZES, Zollinger-Ellison syndrome.

SUPPLEMENTAL REFERENCES

1. Wautot V, Vercherat C, Lespinasse J, Chambe B, Lenoir GM, Zhang CX, et al. Germline mutation profile of MEN1 in multiple endocrine neoplasia type 1: search for correlation between phenotype and the functional domains of the MEN1 protein. *Hum Mutat* 2002;20:35-47.
2. Hasani-Ranjbar S, Amoli MM, Ebrahim-Habibi A, Gozashti MH, Khalili N, Sayyapour FA, et al. A new frameshift MEN1 gene mutation associated with familial malignant insulinomas. *Fam Cancer* 2011;10:343-8.
3. Morelli A, Falchetti A, Martinetti V, Becherini L, Mark M, Friedman E, et al. MEN1 gene mutation analysis in Italian patients with multiple endocrine neoplasia type 1. *Eur J Endocrinol* 2000;142:131-7.
4. Giraud S, Zhang CX, Serova-Sinilnikova O, Wautot V, Sallandre J, Buisson N, et al. Germ-line mutation analysis in patients with multiple endocrine neoplasia type 1 and related disorders. *Am J Hum Genet* 1998;63:455-67.
5. Chung YJ, Hwang S, Jeong JJ, Song SY, Kim SH, Rhee Y. Genetic and epigenetic analysis in Korean patients with multiple endocrine neoplasia type 1. *Endocrinol Metab (Seoul)* 2014;29:270-9.
6. Kouvaraki MA, Lee JE, Shapiro SE, Gagel RF, Sherman SI, Sellin RV, et al. Genotype-phenotype analysis in multiple endocrine neoplasia type 1. *Arch Surg* 2002;137:641-7.
7. Lemmens I, Van de Ven WJ, Kas K, Zhang CX, Giraud S, Wautot V, et al. Identification of the multiple endocrine neoplasia type 1 (MEN1) gene. The European Consortium on MEN1. *Hum Mol Genet* 1997;6:1177-83.
8. Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 1997;276:404-7.
9. Crepin M, Escande F, Pigny P, Buisine MP, Calender A, Porchet N, et al. Efficient mutation detection in MEN1 gene using a combination of single-strand conformation polymorphism (MDGA) and heteroduplex analysis. *Electrophoresis* 2003;24:26-33.
10. Schaaf L, Pickel J, Zinner K, Hering U, Hofler M, Goretzki PE, et al. Developing effective screening strategies in multiple endocrine neoplasia type 1 (MEN 1) on the basis of clinical and sequencing data of German patients with MEN 1. *Exp Clin Endocrinol Diabetes* 2007;115:509-17.
11. Agarwal SK, Debelenko LV, Kester MB, Guru SC, Manickam P, Olufemi SE, et al. Analysis of recurrent germline mutations in the MEN1 gene encountered in apparently unrelated families. *Hum Mutat* 1998;12:75-82.
12. Cebrian A, Ruiz-Llorente S, Cascon A, Pollan M, Diez JJ, Pico A, et al. Mutational and gross deletion study of the MEN1 gene and correlation with clinical features in Spanish patients. *J Med Genet* 2003;40:e72.
13. Bhai P, Levy MA, Rooney K, Carere DA, Reilly J, Kerkhof J, et al. Analysis of sequence and copy number variants in canadian patient cohort with familial cancer syndromes using a unique next generation sequencing based approach. *Front Genet* 2021;12:698595.
14. Hai N, Aoki N, Matsuda A, Mori T, Kosugi S. Germline MEN1 mutations in sixteen Japanese families with multiple endocrine neoplasia type 1 (MEN1). *Eur J Endocrinol* 1999;141:475-80.
15. Tham E, Grandell U, Lindgren E, Toss G, Skogseid B, Nordenskjold M. Clinical testing for mutations in the MEN1 gene in Sweden: a report on 200 unrelated cases. *J Clin Endocrinol Metab* 2007;92:3389-95.
16. Poncin J, Abs R, Velkeniers B, Bonduelle M, Abramowicz M, Legros JJ, et al. Mutation analysis of the MEN1 gene in Belgian patients with multiple endocrine neoplasia type 1 and related diseases. *Hum Mutat* 1999;13:54-60.
17. Gortz B, Roth J, Speel EJ, Krahenmann A, De Krijger RR, Matias-Guiu X, et al. MEN1 gene mutation analysis of sporadic adrenocortical lesions. *Int J Cancer* 1999;80:373-9.
18. Marini F, Giusti F, Fossi C, Cioppi F, Cianferotti L, Masi L, et al. Multiple endocrine neoplasia type 1: analysis of germline MEN1 mutations in the Italian multicenter MEN1 patient database. *Endocrine* 2018;62:215-33.
19. Jamilloux Y, Favier J, Pertuit M, Delage-Corre M, Lopez S, Teissier MP, et al. A MEN1 syndrome with a paraganglioma. *Eur J Hum Genet* 2014;22:283-5.
20. Toliat MR, Berger W, Ropers HH, Neuhaus P, Wiedenmann B. Mutations in the MEN I gene in sporadic neuroendocrine tumours of gastroenteropancreatic system. *Lancet* 1997;350:1223.
21. Concolino P, Costella A, Capoluongo E. Multiple endocrine neoplasia type 1 (MEN1): an update of 208 new germline variants reported in the last nine years. *Cancer Genet* 2016;209:36-41.
22. Horiuchi K, Okamoto T, Iihara M, Tsukada T. Analysis of genotype-phenotype correlations and survival outcomes in patients with primary hyperparathyroidism caused by multiple endocrine neoplasia type 1: the experience at a single institution. *Surg Today* 2013;43:894-9.

23. Park JH, Kim IJ, Kang HC, Lee SH, Shin Y, Kim KH, et al. Germline mutations of the MEN1 gene in Korean families with multiple endocrine neoplasia type 1 (MEN1) or MEN1-related disorders. *Clin Genet* 2003;64:48-53.
24. Agarwal SK, Kester MB, Debelenko LV, Heppner C, Emmert-Buck MR, Skarulis MC, et al. Germline mutations of the MEN1 gene in familial multiple endocrine neoplasia type 1 and related states. *Hum Mol Genet* 1997;6:1169-75.
25. Han B, Song ZY, Wu JJ, Liu W, Liu BL, Ye XP, et al. A novel intronic mutation and a missense mutation of MEN1 identified in two Chinese families with multiple endocrine neoplasia type 1. *J Endocrinol Invest* 2013;36:162-7.
26. Choi H, Kim S, Moon JH, Lee YH, Rhee Y, Kang ES, et al. Multiple endocrine neoplasia type 1 with multiple leiomyomas linked to a novel mutation in the MEN1 gene. *Yonsei Med J* 2008;49:655-61.
27. Kwon EB, Jeong HR, Shim YS, Lee HS, Hwang JS. Multiple endocrine neoplasia type 1 presenting as hypoglycemia due to insulinoma. *J Korean Med Sci* 2016;31:1003-6.
28. Shimizu S, Tsukada T, Futami H, Ui K, Kameya T, Kawana M, et al. Germline mutations of the MEN1 gene in Japanese kindred with multiple endocrine neoplasia type 1. *Jpn J Cancer Res* 1997;88:1029-32.
29. Backman S, Bajic D, Crona J, Hellman P, Skogseid B, Stalberg P. Whole genome sequencing of apparently mutation-negative MEN1 patients. *Eur J Endocrinol* 2020;182:35-45.
30. Turner JJ, Leotlela PD, Pannett AA, Forbes SA, Bassett JH, Harding B, et al. Frequent occurrence of an intron 4 mutation in multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 2002;87:2688-93.
31. ClinVar. NM_001370259.2(MEN1):c.1471G>T (p.Glu491Ter) [Internet]. Bethesda: National Library of Medicine; 2024 [cited 2024 Sep 21]. Available from: [https://www.ncbi.nlm.nih.gov/clinvar/variation/1998541/?oq=1998541&m=NM_001370259.2\(MEN1\):c.1471G%3ET%20\(p.Glu491Ter\)](https://www.ncbi.nlm.nih.gov/clinvar/variation/1998541/?oq=1998541&m=NM_001370259.2(MEN1):c.1471G%3ET%20(p.Glu491Ter)).
32. Morelli A, Falchetti A, Martinetti V, Becherini L, Mark M, Friedman E, et al. MEN1 gene mutation analysis in Italian patients with multiple endocrine neoplasia type 1. *Eur J Endocrinol* 2000;142:131-7.
33. Bartsch D, Kopp I, Bergenfelz A, Rieder H, Deiss Y, Munch K, et al. Keimbahnmutationen im MEN1-Gen: basis für prädiagnostisches genetisches screening und klinisches management von MEN1-familien [Germline mutations in the MEN1 gene: basis for predictive genetic screening and clinical management of multiple endocrine neoplasia type 1 (MEN1) families]. *Dtsch Med Wochenschr* 1998;123:1535-40.
34. Seo GH, Kim T, Choi IH, Park JY, Lee J, Kim S, et al. Diagnostic yield and clinical utility of whole exome sequencing using an automated variant prioritization system, EVIDENCE. *Clin Genet* 2020;98:562-70.
35. van Asselt SJ, Brouwers AH, van Dullemen HM, van der Jagt EJ, Bongaerts AH, Kema IP, et al. EUS is superior for detection of pancreatic lesions compared with standard imaging in patients with multiple endocrine neoplasia type 1. *Gastrointest Endosc* 2015;81:159-67.e2.