

Supplementary Table S1: Gene-dose response relationship comparison (wildtype vs heterozygous vs homozygous) in hereditary MTC group (n=77).

SNPs	Age at MTC diagnosis; Median (n)				Calcitonin levels at diagnosis; Median (n)				Tumor Volume; cm ³ ;Median (n)				Lymph Node metastasis (n)				Distant Metastasis (n)			
	Wt (n)	Hz (n)	Hm (n)	p	Wt (n)	Hz (n)	Hm (n)	p	Wt (n)	Hz (n)	Hm (n)	p	Wt (n)	Hz (n)	Hm (n)	p	Wt (n)	Hz (n)	Hm (n)	p
RET G691S	31 (37)	38 (29)	21 (9)	0.06	1807 (23)	3397 (23)	1076 (5)	0.43	5.3 (10)	2.1 (16)	4.6 (5)	0.5	26 (28)	16 (20)	6 (7)	0.42	11 (27)	7 (18)	1 (7)	0.41
RET L769L	34 (33)	31 (33)	31 (9)	0.89	2243 (25)	2937 (23)	1101 (3)	0.92	2.1 (17)	6.0 (13)	12 (1)	0.27	24 (26)	19 (23)	5 (6)	0.56	8 (24)	8 (22)	3 (6)	0.75
RET S836S	31 (62)	34 (13)	0 (0)	0.59	2590 (44)	1670 (7)	0 (0)	0.96	4.6 (28)	1.4 (3)	0 (0)	0.3	45 (51)	3 (4)	0 (0)	0.44	17 (48)	2 (4)	0 (0)	0.56
RET S904S	31 (36)	36 (28)	21 (11)	0.07	2937 (23)	2243 (23)	1076 (5)	0.32	6.1 (10)	2.0 (14)	3.0 (7)	0.36	24 (26)	16 (20)	8 (9)	0.45	11 (26)	7 (18)	1 (8)	0.3
Cyp1A1ml	32 (35)	31 (36)	25 (4)	0.7	5859 (24)	1522 (26)	2937 (1)	0.1	3.8 (16)	2.1 (13)	4.7 (2)	0.83	22 (23)	25 (29)	1 (3)	0.01	9 (22)	10 (28)	0 (2)	0.51
Cyp1A2*F	31 (28)	30 (33)	39 (14)	0.22	3403 (17)	1753 (24)	6546 (10)	0.66	6.2 (10)	1.4 (17)	5.6 (4)	0.23	19 (21)	21 (25)	8 (9)	0.79	8 (18)	5 (24)	6 (10)	0.07
NAT2	32 (31)	31 (32)	29 (12)	0.77	2702 (18)	2437 (24)	1699 (9)	0.99	2.1 (13)	4.5 (15)	2.0 (3)	0.98	21 (23)	18 (22)	9 (10)	0.61	9 (22)	7 (20)	3 (10)	0.82
GSTP1	32 (34)	30 (34)	39 (7)	0.75	1716 (24)	3403 (23)	770 (4)	0.32	1.3 (11)	7.5 (16)	3.3 (4)	0.15	21 (24)	23 (27)	4 (4)	0.71	12 (25)	6 (24)	1 (3)	0.25
CDKN1A	31 (63)	31 (11)	35 (1)	0.74	1753 (42)	4443 (8)	3403 (1)	0.48	2.0 (26)	7.5 (4)	2.1 (1)	0.31	36 (43)	11 (11)	1 (1)	0.32	13 (41)	6 (10)	0 (1)	0.18
CDKN1B	31 (34)	31 (32)	32 (9)	0.76	3403 (23)	1753 (22)	15175 (6)	0.59	6.2 (14)	2.0 (13)	1.0 (4)	0.21	21 (23)	22 (26)	5 (6)	0.74	7 (21)	9 (25)	3 (6)	0.75
CDKN2A	31 (65)	30 (7)	23 (3)	0.6	2090 (42)	2484 (6)	2937 (3)	0.84	5.3 (24)	1.5 (5)	0.3 (2)	0.16	42 (46)	5 (6)	1 (3)	0.01	18 (43)	1 (6)	0 (3)	0.19
CDKN2B	31 (46)	31 (25)	28 (4)	0.66	3049 (30)	1237 (18)	3403 (3)	0.38	5.3 (16)	2.0 (11)	3.3 (4)	0.76	27 (33)	17 (18)	4 (4)	0.34	11 (31)	8 (18)	0 (3)	0.32
CDKN2C	31 (62)	31 (12)	23 (1)	0.56	2702 (40)	1672 (10)	2937 (1)	0.95	4.5 (25)	2.0 (5)	0.4 (1)	0.57	38 (44)	10 (10)	0 (1)	0.01	13 (40)	6 (11)	0 (1)	0.3

Supplementary Table S2: Gene-dose response relationship comparison (wildtype vs heterozygous vs homozygous) in sporadic MTC group (n=361)

SNPs	Age at MTC diagnosis; Median (n)				Calcitonin levels at diagnosis; Median (n)				Tumor Volume; cm ³ ; Median (n)				Lymph Node metastasis (n)				Distant Metastasis (n)			
	Wt (n)	Hz (n)	Hm (n)	p	Wt (n)	Hz (n)	Hm (n)	p	Wt (n)	Hz (n)	Hm (n)	p	Wt (n)	Hz (n)	Hm (n)	p	Wt (n)	Hz (n)	Hm (n)	p
	RET G691S	41 (199)	42 (129)	44 (29)	0.42	3334 (123)	2727 (68)	1673 (16)	0.65	4.9 (120)	7.8 (73)	2.5 (8)	0.17	143 (170)	75 (95)	20 (21)	0.17	50 (145)	33 (80)	6 (15)
RET L769L	42 (145)	40 (170)	40 (42)	0.41	2300 (85)	3008 (101)	5000 (21)	0.24	6.9 (73)	5.9 (100)	3.2 (28)	0.12	99 (113)	108 (137)	31 (36)	0.16	34 (94)	42 (112)	13 (34)	0.97
RET S836S	42 (307)	38 (46)	33 (4)	0.32	3008 (181)	3631 (25)	9367 (1)	0.67	5.8 (173)	5.0 (25)	2.8 (3)	0.41	206 (247)	30 (35)	2 (4)	0.19	78 (205)	11 (31)	0 (4)	0.29
RET S904S	40 (192)	42 (131)	44 (34)	0.29	3295 (122)	2727 (66)	2805 (19)	0.46	5.1 (118)	7.6 (70)	2.8 (13)	0.31	138 (165)	76 (96)	24 (25)	0.13	49 (140)	31 (82)	9 (18)	0.45
Cyp1A1m1	42 (159)	41 (173)	39 (25)	0.75	3008 (101)	2668 (94)	12094 (12)	0.32	6.0 (93)	5.4 (94)	2.3 (14)	0.38	105 (128)	118 (140)	15 (18)	0.88	43 (111)	40 (112)	6 (17)	0.89
Cyp1A2*F	41 (116)	42 (174)	40 (67)	0.89	2532 (69)	3415 (96)	4403 (42)	0.76	5.0 (67)	5.6 (92)	6.3 (42)	0.81	78 (91)	115 (136)	45 (59)	0.27	23 (79)	46 (114)	20 (47)	0.19
NAT2	41 (102)	41 (181)	42 (74)	0.54	2512 (62)	3298 (97)	2692 (48)	0.93	5.9 (54)	4.5 (101)	7.0 (46)	0.21	64 (75)	117 (145)	57 (66)	0.5	29 (66)	39 (117)	21 (57)	0.36
GSTP1	40 (206)	43 (127)	42 (24)	0.74	2692 (116)	4500 (78)	2922 (13)	0.53	4.7 (120)	8.8 (71)	4.5 (10)	0.22	132 (161)	88 (104)	18 (21)	0.81	49 (133)	31 (86)	9 (21)	0.84
CDKN1A	42 (291)	35 (66)	0 (0)	0.06	3402 (176)	1571 (31)	0 (0)	0.16	5.9 (157)	4.9 (44)	0 (0)	0.86	198 (234)	40 (52)	0 (0)	0.18	75 (196)	14 (44)	0 (0)	0.42
CDKN1B	43 (179)	39 (152)	39 (26)	0.14	2580 (111)	3511 (84)	3276 (12)	0.87	5.0 (97)	6.3 (87)	4.0 (17)	0.45	123 (144)	98 (121)	17 (21)	0.61	51 (120)	30 (101)	8 (19)	0.13
CDKN2A	42 (306)	40 (47)	42 (4)	0.89	3277 (170)	1970 (33)	1745 (4)	0.88	6.0 (169)	3.0 (29)	8.0 (3)	0.21	200 (244)	34 (38)	4 (4)	0.34	72 (199)	15 (37)	2 (4)	0.76
CDKN2B	42 (204)	40 (124)	43 (29)	0.46	2805 (119)	4670 (71)	1230 (17)	0.29	6.5 (112)	5.1 (72)	4.5 (17)	0.26	141 (167)	83 (99)	14 (20)	0.26	54 (137)	30 (85)	5 (18)	0.57
CDKN2C	42 (293)	39 (59)	40 (5)	0.49	3373 (167)	1593 (36)	6839 (4)	0.27	5.2 (167)	5.6 (32)	22.9 (2)	0.88	198 (236)	38 (45)	2 (5)	0.03	74 (200)	15 (36)	0 (4)	0.26