

## Supplementary-

**Supplementary Table S1: List of the genes reported to have mutations causing familial non-medullary thyroid cancer.**

Gene	Protein	OMIM	Reference
<b>ANXA3</b>	Annexin A3	106490	1
<b>ATM</b>	Ataxia Telangiectasia Mutated	607585	2
<b>BRCA1</b>	Breast cancer type 1 susceptibility protein	113705	2
<b>CHEK2</b>	Checkpoint Kinase 2	604373	2,3
<b>CIAO3</b>	Cytosolic Iron-Sulfur Assembly Component 3	611118	4
<b>DICER1</b>	Endoribonuclease Dicer	606241	2,4
<b>EIF1AX</b>	Eukaryotic Translation Initiation Factor 1A X-Linked	300186	3
<b>FKBP10</b>	Peptidyl-prolyl cis-trans isomerase	607063	1
<b>FOXE1</b>	Forkhead box protein E1	602617	2,4
<b>HABP2</b>	Hyaluronan Binding Protein 2	603924	2,4,5
<b>MYH9</b>	Myosin Heavy Chain 9	160775	2
<b>NKX2.1</b>	Homeobox protein Nkx-2.1	600635	2,4,6
<b>NMTC1</b>	Non-medullary thyroid carcinoma 1	606240	4
<b>NTN4</b>	Netrin 4	610401	1
<b>P2RX5</b>	Purinergic Receptor P2X 5	602836	1
<b>PLEKHG5</b>	Pleckstrin Homology And RhoGEF Domain Containing G5	611101	1
<b>PPM1D</b>	Protein Phosphatase, Mg2+/Mn2+ Dependent 1D	605100	3
<b>PTCSC2</b>	Papillary Thyroid Carcinoma Susceptibility Candidate 2	44086*	2
<b>PTCSC3</b>	Papillary Thyroid Carcinoma Susceptibility Candidate 3	614821	2
<b>RASAL1</b>	RAS Protein Activator Like 1	604118	2
<b>SAPCD1</b>	Suppressor APC Domain Containing 1	13938*	1
<b>SERPINA1</b>	Serpin Family A Member 1	107400	1
<b>SLC34A2</b>	Solute Carrier Family 34 Member 2	604217	7
<b>SPRY4</b>	Sprouty RTK Signaling Antagonist 4	607984	8
<b>SRGAP1</b>	SLIT-ROBO Rho GTPase Activating Protein 1	606523	2,4
<b>SRRM2</b>	Serine/Arginine Repetitive Matrix 2	606032	2,9
<b>TCO</b>	Thyroid carcinoma, non-medullary, with cell oxyphilia	603386	4
<b>TRPM3</b>	Transient Receptor Potential Cation Channel Subfamily M Member 3	608961	6
<b>WDR77</b>	WD Repeat Domain 77	611734	10
<b>XRCC1</b>	X-Ray Repair Cross Complementing 1	194360	2
<b>OMIM: Online Mendelian Inheritance in Man. *HUGO Gene Nomenclature Committee (HGNC)</b>			

**Supplementary Table S2: Family segregation analysis of the 50 negated candidate variants while comparing exome sequencing of patients – III8, III10, IVA5, XFIII4, and XFIII5.**

Gene Symbol	Position	Ref/Alt	III1 A	III2 H	III4 H	III5 A	III6 H	III8 A	III10 A	IVA5 A	XFIII1 A	XFIII4 A	XFIII5 A
<i>MSH6</i>	chr2:48033423	A>T	-/+	+/+	+/+	-/+	-/-	-/+	-/+	-/+	-	+/+	+/+
<i>LATS1</i>	chr6:150023177	A>G	+/+	-	-	+/+	-	-/+	-/+	-/+	-	+/+	+/+
<i>ITGAX</i>	chr16:31388180	G>A	-/+	+/+	+/+	+/+	+/+	-/+	-/+	-/+	-	+/+	+/+
<i>GNAS</i>	chr20:57429715	A>C	-	-	-	+/+	-	+/+	+/+	+/+	-	+/+	+/+
<i>F7</i>	chr13:113772751	A/G	-/+	-/+	-/+	-/+	+/+	-/+	-/+	-/+	-	+/+	-/+
<i>ATM</i>	chr11:108172382	G/C	-/+	-	-	+/+	-	-/+	-/+	-/+	-	+/+	+/+
<i>PEX26</i>	chr22:18567998	G/C	-/+	-	-	+/+	-	-/+	-/+	-/+	-	+/+	+/+
<i>QSER1</i>	chr11:32953759	A/G	+/+	-	-	+/+	-	-/+	-/+	-/+	-	-/+	-/+
<i>HSPG2</i>	chr1:22157748	C/G	+/+	-	-	-/+	-	-/+	-/+	-/+	-	+/+	+/+
<i>FCHSD1</i>	chr5:141024648	G/A	-/+	-	-	+/+	-	-/+	-/+	-/+	-	+/+	+/+
<i>FAM160A1</i>	chr4:152559873	A/T	-/+	-	-	+/+	-	-/+	+/+	-/+	-	+/+	+/+
<i>PIEZO2</i>	chr18:10677856	C/T	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-	-/+	-/+
<i>BCR</i>	chr22:23524386	C/G	-/+	+/+	-/-	-/+	+/+	-/+	-/+	-/+	-	+/+	+/+
<i>ATR</i>	chr3:142268341	C>T	-	-	-	-	-	+/+	+/+	+/+	-	+/+	+/+
<i>RSC1A1</i>	chr1:15986365	T>C	-	-	-	-	-	+/+	+/+	+/+	-	+/+	+/+
<i>TERT</i>	chr5:1294163	G>A	-	-	-	-	-	+/+	+/+	+/+	-	+/+	+/+
<i>CUL9</i>	chr6:43152097	C>T	-	-	-	-	-	+/+	+/+	+/+	-	+/+	+/+
<i>SOC5</i>	chr2:46985961	A>C	-	-	-	-	-	+/+	+/+	+/+	-	+/+	+/+
<i>BRCA2</i>	chr13:32913690	C>T	-	-	-	-	-	+/+	+/+	+/+	-	+/+	+/+
<i>CLDN10</i>	chr13:96212695	G>A	-	-	-	-	-	+/+	+/+	+/+	-	+/+	+/+
<i>SHPRH</i>	chr6:146269484	delGAA	-	-	-	+/+	-	-/+	-/+	-/+	-	-/+	+/+
<i>NID2</i>	chr14:52505546	G>A	-	-	-	-	-	-/+	-/-	-/+	-	-/+	+/+
<i>FMO2</i>	chr1:171173065	C>T	-/+	-	-	+/+	-	-/+	-/+	-/+	-	-/+	-/+
<i>PRKAG3</i>	chr2:219695056	T>A	-/-	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/-	-/+	-/+
<i>ABCA12</i>	chr2:215919360	G>T	-/-	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/-	-/+	-/+
<i>CCDC108</i>	chr2:219868816	A>G	-/-	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/-	-/+	-/+
<i>NDST4</i>	chr4:115898360	G>C	-/+	+/+	-/+	-/+	+/+	-/+	-/+	-/+	-/+	-/+	+/+
<i>CENPE</i>	chr4:104030085	G>A	-/+	-	-	-	-	-/+	-/+	-/+	-/+	-/+	+/+
<i>DCHS2</i>	chr4:155163847	T>A	-/+	-/+	-	+/+	+/+	-/+	+/+	-/+	+/+	-/+	-/+
<i>MDFI</i>	chr6:41613864	C>T	-/+	-	-	-/+	-	-/+	+/+	-/+	-	-/+	+/+
<i>PRRG4</i>	chr11:32874843	T>A	+/+	+/+	+/+	+/+	+/+	-/+	-/+	-/+	+/+	-/+	-/+
<i>QSER1</i>	chr11:32953759	A>G	+/+	-	-	+/+	-	-/+	-/+	-/+	-	-/+	-/+
<i>TBX5</i>	chr12:114793375	G>A	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/+	+/+	-/+	-/+
<i>SPNS2</i>	chr17:4402454	G>T	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/+
<i>STK11IP</i>	chr2:220470710	G>A	-/-	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/-	-/+	-/+
<i>SMOC2</i>	chr6:169064783	A>G	-/+	-/-	-/+	-/-	-/+	-/-	-/+	-/-	-/+	-/+	-/+
<i>SLC26A7</i>	chr8:92375732	A>T	-/+	-	-	+/+	-	-/+	-/+	-/+	+/+	-/+	-/+
<i>HECW2</i>	chr2:197183394	G>C	-/+	-/-	-/-	-/-	-/+	-/-	-/-	-/+	-/+	-/+	-/+
<i>TP53I13</i>	chr17:27899895	C>T	-/+	-	-	-/-	-	-/+	-/+	-/+	+/+	-/+	-/+
<i>LOXL2</i>	chr8:23225582	G>A	-/+	-	-	+/+	-	-/+	+/+	-/+	-/+	-/+	-/+

<b>GPR124</b>	chr8:37697775	C>T	-/+	-	-	+/+	-	-/+	+/+	-/+	-/+	-/+	-/+
<b>EFCAB5</b>	chr17:28380799	delAG	-/+	-	-		-	-/+	-/+	-/+	+/+	-/+	-/+
<b>CBFA2T3</b>	chr16:88947694	G>A	-/+	-	-	+/+	-	-/+	-/+	-/+	+/+	-/+	-/+
<b>SLC28A2</b>	chr15:45559861	C>T	-/+	-	-	-/+	-	-/+	+/+	-/-	-/+	-/+	-/+
<b>PPP6R2</b>	chr22:50876272	T>C	-/+	-	-	+/+	-	-/+	-/+	-/+	-/+	-/+	+/+
<b>CFAP65</b>	chr2:219868816	A>G	-/-	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/-	-/+	-/+
<b>MSRB3</b>	chr12:65857067	G>A	-/+	-	-	-/+	-	-/+	-/+	-/-	+/+	-/+	-/+
<b>KIF24</b>	chr9:34269296	A>G	-/+	-	-	-/+	-	-/+	-/+	-/+	+/+	-/+	-/+
<b>FIGNL2</b>	chr12:52214855	A>G	-/+	-	-	-/+	-	-/+	-/+	-/-	+/+	-/+	-/+
<b>SPAG5</b>	chr17:26911215	C>A	-/+	-	-	-/-	-	-/+	-/+	-/+	+/+	-/+	-/+

The family members' annotations are according to Figure 1. -/-: homozygote for the mutation; -/+: heterozygote, and +/+: normal. "A" represents affected PTC individuals, and "H" represents healthy individuals. Positions on chromosomes are according to GRCh37/hg19.

**Supplementary Table S3: The analysis of the protein-protein interactions (PPI) detected by the Biological General Repository for Interaction Datasets (BioGRID).**

Protein	Interactor	Organism	Experimental Evidence	Reference
<b>ARHGEF28</b>	<b>SQSTM1</b>	H. sapiens	Affinity Capture-Western	11
<b>ARHGEF28</b>	<b>MYH9</b>	H. sapiens	Proximity Label-MS	12
<b>SQSTM1</b>	<b>TP53</b>	H. sapiens	Affinity Capture-Western Reconstituted Complex	13–17
<p><b>Affinity Capture-Western:</b> An interaction is inferred when a bait protein is affinity captured from cell extracts by either polyclonal antibody or epitope tag and the associated interaction partner identified by Western blot with a specific polyclonal antibody or second epitope tag. <b>Proximity Label-MS:</b> An interaction is inferred when a bait-enzyme fusion protein selectively modifies a vicinal protein with a diffusible reactive product, followed by affinity capture of the modified protein and identification by mass spectrometric methods. <b>Reconstituted Complex:</b> An interaction is detected between purified proteins in vitro.</p>				

**Supplementary Table S4: The primers that were used for the PCR amplification.**

Primers	T <sub>m</sub> (c°)	Product size (bp)
HABP2-F (1): 5' CCCCAGAGAACTCACAGTCAT 3' HABP2-R (1): 5' CTGGTGATATTGTGCAAATGCT 3'	62	646
HABP2-F (2): 5' AGACTTGGGACCGCTTTCTT 3' HABP2-R (2): 5' GTGCAGACAGTTGGGCAGT 3'	62	492
MSH6-F: 5' AACCGATGTTGCTTTTCTGTC 3' MSH6-R: 5' CCATGCATGCCTTAAGAAAGA 3'	62	355
LATS1-F: 5' GTCCTTCGTGTGGGCTACAT 3' LATS1-R: 5' GTCGAGGATCTTCGGTTGAC 3'	62	224
GNAS-F: 5' GGCAACCCAGAAAGATCC 3' GNAS-R: 5' TCTGAGATGGATCTTGCGTCT 3'	63	373
ITGAX-F: 5' TCACTACTTCGTGGCGTGTC 3' ITGAX-R: 5' GAAGGTGATCTGAGGAAAAGGA 3'	62	328
ATM-F: 5' CAGTGGAGGTAAACATTCATCAAG 3' ATM-R: 5' GTCATGACCCACAGCAAACA 3'	63	284
F7-F: 5' CCAGATTCACCCAGTTCAC 3' F7-R: 5' CACCACATGGTCAGTGAGGA 3'	63	364
PEX26-F: 5' ACATCCCTGAAGCTGTGCTC 3' PEX26-R: 5' GAGACTCCCTCCCCAGTAG 3'	63	288
QSER1-F: 5' CAACATACCGCTCAGCTCAA 3' QSER1-R: 5' GGAGTGCTGTGAACCAGTCA 3'	62	239
HSPG2-F: 5' GAGCAGCGGCTTCATAG <sub>gt</sub> 3' HSPG2-R: 5' GCCGAGAACATTCAGTACCC 3'	62	364
FCHSD1-F: 5' GCCCCATATGAGGTCTGTTC 3' FCHSD1-R: 5' CACCCCCATTACATACCTGAT 3'	62	177
FAM160A1-F: 5' CGTTCCAACATCTGAAGTAGAATG 3' FAM160A1-R: 5' TTGGCGCCTTTTATAGCTTAT 3'	61	249
FBXW10-F: 5' TGGGATCAAAACCGAGTCAT 3' FBXW10-R: 5' TTCTTCCATGAGCTGCCTCT 3'	62	265
PIZO2-F: 5' CCAATGAAAACGTGGTGACA 3' PIZO2-R: 5' CTGTGCTGTTGCCTGCTATC 3'	63	220
BCR-F: 5' CAACAGTCCTTCGACAGCAG 3' BCR-R: 5' ACGTGGCGTGAGGAACTC 3'	62	177
ATR-F: 5' GCTTCTGCTCTCATTCGAACTT 3' ATR-R: 5' CACCCTCTTTCCTAGAAGAATGTT 3'	62	229
CLDN10-F: 5' CACTAACCATAGTGCTTTCCCTCT 3' CLDN10-R: 5' GGAAATTCATGTCTCTTGGTTGA 3'	62	199
NR4A1-F: 5' TATATGTGCGGGGTCCTGGAA 3' NR4A1-R: 5' TGCCTAATGCAGACATCACC 3'	62	220
CUL9-F: 5' ATTCCACCCCTCCATGTAT 3' CUL9-R: 5' CCACACTCAGGACACTCCA 3'	62	220

SOCS5-F: 5' GCACTGCCTTAGCTACCTTCA 3' SOCS5-R: 5' CAGCATCCAATGAACTCTGG 3'	62	498
TERT-F: 5' AGTGCCAGCCGAAGTCTG 3' TERT-R: 5' GTACACCGGGGACAAGG 3'	63	297
RSC1A1-F: 5' AACCCGAGTTTGAGGACCTT 3' RSC1A1-R: 5' GAGCGAGCAAGACTCATAGGAT 3'	62	245
BRCA2-F: 5' GTCCTGCAACTTGTTACACAAATCA 3' BRCA2-R: 5' AGCTAGTCACAAGTTCCTCAACG 3'	63	501
SHPRH-F: 5' TGTGGCTTTTCCAGAATGAGA 3' SHPRH-R: 5' AATTTTGCCTTACCAGCCTGT 3'	63	237
NID2-F: 5' CTCTCTGACTTTTGGTGCAAT 3' NID2-R: 5' GCATGGCACTAGGTAACCCTTA 3'	61	300
STK11IP-F: 5' GGTCTTTCTGCTGCAACCTC 3' STK11IP-R: 5' CTGATGCATTCCCATCTCAC 3'	62	218
HECW2-F: 5' CGAAGGGTCGCAGGAATC 3' HECW2-R: 5' CTCGAGCCAAGAGCCACAG 3'	65	293
SLC26A7-F: 5' ATCCCCGAATATCCCAGAGA 3' SLC26A7-R: 5' TGCTTTTGTCTGAATGCTGAA 3'	62	475
SMOC2-F: 5' AGTGATGTGGACTCCTTCCTG 3' SMOC2-R: 5' TTCTTGATTTCCTTGGAAGGT 3'	61	242
FMO2-F: 5' CTAAACGGGACAATGCCCTA 3' FMO2-R: 5' CAACTTTGCTCACCAACGAG 3'	62	300
PRKAG3-F: 5' TGTGAGATGAATGGCGACAG 3' PRKAG3-R: 5' GTTCCGCGAGTTCGTCATC 3'	63	387
ABCA12-F: 5' CCCTGGAATCTGCCACATAA 3' ABCA12-R: 5' TGTTCATAAGGCTTGTCTGA 3'	63	221
CCDC108-F: 5' TTAATGCCAATCCTGCCTGT 3' CCDC108-R: 5' CCTTCTCGTCCTGTTCTTGC 3'	62	364
NDST4-F: 5' AGAGGCATCCCCAAACTTCA 3' NDST4-R: 5' CAATCTGGAGAATCTATCTCTACCACT 3'	62	245
CENPE-F: 5' GCATCTTTCCAATGAGGTCAA 3' CENPE-R: 5' TAGCGAACTGGATGAGGTGA 3'	63	246
DCHS2-F: 5' TTGATTGTCCAAGCCACAGA 3' DCHS2-R: 5' AGTTTGCTTGGTTGTTGAGGA 3'	62	246
MDFI-F: 5' GCTCACTCCCAGATTGTGGT 3' MDFI-R: 5' GACGTCGAGGTCAGTGCTGT 3'	64	365
PRRG4-F: 5' TCAAAGCTCTTGGTCTTTCCA 3' PRRG4-R: 5' CCCGGCCTATCAAATAACAC 3'	62	460
TBX5-F: 5' TGGACAGGCTACCCTACCAG 3' TBX5-R: 5' CATCCAGCGACCTTGAGTG 3'	63	457
SPNS2-F: 5' AGGAGGAGGAGGCGGACG 3' SPNS2-R: 5' CGACAGCGTCTGCACCTC 3'	66	140
TRIOBP-F: 5' CAATAGAGCCACACGAGACAA 3' TRIOBP-R: 5' GTTGTCTCGTGCAGCTCTATTG 3'	62	238

TP53I13-F: 5' ACACGGCTGCACAGAACTT 3' TP53I13-R: 5' GTCCACGTGGCAGAGGTC 3'	63	378
LOXL2-F: 5' CAACGTGGCCAAGATTGAG 3' LOXL2-R: 5' GCACTCAGATCCAAAGCACA 3'	63	233
GPR124-F: 5' GGAGGGTCCAGTCGTAGTCC 3' GPR124-R: 5' CAGAAGCCCGCAAGATGT 3'	63	389
EFCAB5-F: 5' AGGACAGCACAAAGGGTCAA 3' EFCAB5-R: 5' GGTCCTTGTTCTGATTTTTGG 3'	62	237
CBFA2T3-F: 5' GACGCCGAGGACACAAAG 3' CBFA2T3-R: 5' GCCCGTGTTTTCTACAAAG 3'	63	239
SLC24A4-F: 5' GGATGTCATCATGGGCATTAC 3' SLC24A4-R: 5' CTCCACAGCAGGACTTGACA 3'	62	208
SLC28A2-F: 5' TGGGAGCCTTCATAGCCTTT 3' SLC28A2-R: 5' GCTTTACCCCTCCTCACTC 3'	63	229
PPP6R2-F: 5' GGGAGTGCCGTCTGATGT 3' PPP6R2-R: 5' ACAGGCCCATGACAGACC 3'	63	298
TMX4-F: 5' TCTGATTCCAGCATCTTACA 3' TMX4-R: 5' GAAAGCAGTCTCAAACAAGCAA 3'	62	264
TBX5-F: 5' GTGTGGGCCTCAGACTGG 3' TBX5-R: 5' GCGACCTTGAGTGCAGATGT 3'	64	297
CFAP65-F: 5' TTAATGCCAATCCTGCCTGT 3' CFAP65-R: 5' CCTTCTCGTCCTGTTCTTGC 3'	62	364
MSRB3-F: 5' CATGCTTTTCCCTGACGTTT 3' MSRB3-R: 5' CACTTTGTTTCCATCACTCTCC 3'	62	232
ARHGEF28-F: 5' CCTCTGCTCGGAAGGTTACTC 3' ARHGEF28-R: 5' AGAACTCCCAACACAGTCCA 3'	62	247
KIF24-F: 5' CACTCCTGCTGTGTCTTTTCTC 3' KIF24-R: 5' CAGTTGCTTTGCTGATTCCA 3'	62	233
FIGNL2-F: 5' GACGAGCAAGATGGTGGACT 3' FIGNL2-R: 5' CTCGCTGATGAGGAGTACGG 3'	63	343
SLC47A1-F: 5' CATGGGGAGGTAATGACTGC 3' SLC47A1-R: 5' CAGCAGATCATGTGCAGTTTC 3'	62	600
SPAG5-F: 5' GCATCCAGGATTTAGGACCA 3' SPAG5-R: 5' CCCTGGGTACAGAGGCTTTT 3'	62	268
<b>T<sub>m</sub>, melting temperature. F, forward primer. R, reverse primer.</b>		

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