Type of file: PDF
Size of file: 0 KB
Title of file for HTML: Supplementary Information
Description: Supplementary Figures, Supplementary Tables and Supplementary References

Type of file: pdf
File size:
Title of file for HTML: Peer Review File
Description:

Supplementary Information

Supplementary Table 1. DTC- or PTC-associated SNPs of a previous European GWAS and replicated SNPs in Asians.

Locus	Gene	SNP	OR	*P*-value	Population	Method	References
9q22.33	*FOXE1*	rs965513	1.75	1.7×10^{-27}	Iceland etc.	GWAS	(1)
			1.65	4.8×10^{-12}	Belarus	GWAS	(2)
			1.69	1.3×10^{-4}	Japanese	SNP	(3)
			1.53	1.4×10^{-4}	Chinese	SNP	(4)
			1.59	4.2×10^{-4}	Japanese	SNP	(5)
		rs7028661	1.64	1.0×10^{-22}	Spain	GWAS	(6)
		rs10122541	1.54	1.1×10^{-17}	Spain	GWAS	(6)
		rs7037324	1.54	1.2×10^{-17}	Spain	GWAS	(6)
14q13.3	*NKX2-1*	rs944289	1.37	2.0×10^{-9}	Iceland etc.	GWAS	(1)
			1.24	1.5×10^{-5}	Spain	GWAS	(6)
			1.21	0.0121	Japanese	SNP	(3)
			1.53	2.2×10^{-10}	Chinese	SNP	(4)
			1.23	0.003	Japanese	SNP	(5)
		rs116909374	2.09	4.6×10^{-11}	Iceland etc.	GWAS	(7)
2q35	*DIRC3*	rs966423	1.34	1.3×10^{-9}	Iceland etc.	GWAS	(7)
			1.31	0.0010	Chinese	SNP	(4)
		rs6759952	1.21	6.4×10^{-10}	Italy etc.	GWAS	(8)
8p12	*NRG1*	rs2439302	1.36	2.0×10^{-9}	Iceland etc.	GWAS	(7)
			1.41	2.78×10^{-5}	Chinese	SNP	(4)
			1.27	0.003	Japanese	SNP	(5)
7q31.1	*IMMP2L*	rs10238549	1.27	4.1×10^{-6}	Italy etc.	GWAS	(8)
		rs7800391	1.25	5.7×10^{-6}	Italy etc.	GWAS	(8)
3q25.32	*RARRES1*	rs7617304	1.25	4.6×10^{-5}	Italy etc.	GWAS	(8)
9q34	*SNAPC4*	rs10781500	1.23	3.5×10^{-5}	Italy etc.	GWAS	(8)
14q24.3	*BATF*	rs10136427	1.40	4.4×10^{-7}	Italy etc.	GWAS	(9)
20q11.23	*DHX35*	rs7267944	1.39	2.1×10^{-8}	Italy etc.	GWAS	(9)
5q14	*ARSB*	rs13184587	1.28	8.5×10^{-6}	Italy etc.	GWAS	(9)
13q12	*SPATA13*	rs1220597	1.26	3.3×10^{-6}	Italy etc.	GWAS	(9)
11p15.3	*GALNTL4*	rs7935113	1.36	7.4×10^{-7}	Italy etc.	GWAS	(10)
20p11	*FOXA2*	rs1203952	1.29	4.4×10^{-6}	Italy etc.	GWAS	(10)
10q26.12	*WDR11-AS1*	rs2997312	1.35	1.2×10^{-4}	Spain	GWAS	(6)
		rs10788123	1.26	5.2×10^{-4}	Spain	GWAS	(6)
		rs1254167	1.38	5.9×10^{-5}	Spain	GWAS	(6)
6q14.1	*HTR1B*	rs4075570	0.82	2.0×10^{-4}	Spain	GWAS	(6)

OR, odd ratio; SNP, single nucleotide polymorphism.

Supplementary Table 2. Descriptive characteristics of the participants.

Characteristics	Total (joint)	Stage 1 (discovery)	Stage 2 (replication)
Cases			
Number	1085	470	615
Age, years ± SD	46.5 ± 12.1	43.9 ± 12.8	48.4 ± 11.1
Male %	14.4 %	13.0 %	15.4 %
Pathology			
PTC:FTC, *N* (%)	997:88 (91.9:8.1)	410:60 (87.2:12.8)	587:28 (95.4:4.6)
$BRAF^{V600E}$ in PTC (%)	186/215 (86.5)	186/215 (86.5)	-
LN metastasis in PTC (%)	419/827 (50.7)	186/337 (55.2)	233/490 (47.6)
Distant metastasis in PTC (%)	5/769 (0.7)	2/338 (0.6)	3/431 (0.7)
ETE in PTC (%)	519/886 (58.6)	221/377(58.6)	298/509 (58.5)
Controls			
Number	8884	8279	605
Age, years ± SD	52.6 ± 8.8	52.1 ± 8.9	58.9 ± 4.3
Male %	47.5 %	45.2 %	79.2 %

ETE, extrathyroidal extension; LN, lymph node; SD, standard deviation.

Supplementary Table 3. Forty-one candidate SNPs for stage 2 follow-up study.

Chr	SNP	Position*	Genes	Risk alelle	Allele frequency in Cases	Allele frequency in Controls	OR	*P*-value†	SNP selection Criteria‡
1	rs57075645	99862185	87kb 3' of *LPPR4*	A	0.101	0.060	1.76	3.81E-07	a
1	rs4915076	108359505	Intronic *VAV3*	C	0.233	0.301	0.71	9.37E-06	a
1	rs4649295	233416538	Intronic *PCNXL2*	T	0.124	0.180	0.64	1.04E-05	a
2	rs2121260	38268763	intronic *FAM82A1*	G	0.169	0.125	1.43	8.34E-05§	a
2	rs1979142	39032703	intronic *DHX57*	G	0.187	0.132	1.51	1.76E-06	a
2	rs1549738	218118722	30kb 3' of *DIRC3*	G	0.388	0.448	0.78	2.96E-04	c
2	rs12990503	218294217	intronic *DIRC3*	G	0.315	0.375	0.76	1.82E-04	c
3	rs9858271	59545330	190kb 3' of *FHIT*	G	0.503	0.426	1.37	3.57E-06	a
4	rs1874564	77858105	13kb 5' of *SEPT11*	A	0.233	0.305	0.69	3.43E-06	a
4	rs6841841	182790626	270kb 3' of *MGC45800*	G	0.166	0.232	0.66	3.68E-06	a
5	rs10941849	20719433	731kb 5' of *CDH18*	T	0.082	0.044	1.96	5.11E-08	a
5	rs10447240	119328679	357kb 3' of *FAM170A*	A	0.082	0.047	1.36	2.26E-05§	a
6	rs16889600	78723162	550kb 5' of *HTR1B*	T	0.556	0.484	1.83	9.34E-07	c
6	rs9361385	78926958	650kb 5' of *IRAK1BP1*	C	0.043	0.022	1.34	1.57E-05	a
6	rs11754852	92261591	30kb 3' of *MIR4643*	C	0.013	0.049	1.99	3.83E-05§	a
7	rs2952745	52196144	812kb 5' of *COBL*	T	0.372	0.302	0.25	4.74E-07	a
7	rs2715152	82457666	intronic *PCLO*	G	0.069	0.116	1.37	6.24E-06	a
8	rs36041430	24199218	missense *ADAM28*	A	0.324	0.253	0.57	1.72E-05	a
8	rs12542743	32318355	intronic *NRG1*	C	0.300	0.225	1.42	1.12E-06	a
8	rs6996585	32400803	intronic *NRG1*	G	0.261	0.190	1.48	1.20E-07	a
8	rs2439302	32432369	intronic *NRG1*	G	0.269	0.213	1.36	8.38E-05	b
8	rs11778356	55387405	14kb 3' of *SOX17*	A	0.284	0.228	1.51	1.20E-07	a
9	rs4628781	18795997	intronic *ADAMTSL1*	C	0.070	0.038	1.35	6.81E-05§	a
9	rs10867527	83023162	682kb 3' of *TLE4*	G	0.115	0.067	1.93	6.62E-07	a
9	rs1588635	100537802	78kb 5' of *FOXE1*	A	0.168	0.123	1.81	1.74E-08	a
9	rs7028661	100538470	77kb 5' of *FOXE1*	A	0.115	0.067	1.8	2.52E-08	b
9	rs965513	100556109	59kb 5' of *FOXE1*	A	0.109	0.061	1.91	2.35E-09	b
9	rs1867277	100615914	5'-UTR *FOXE1*	A	0.116	0.075	1.44	4.38E-05	c
9	rs10122541	100628268	9kb 3' of *FOXE1*	G	0.121	0.080	1.57	1.43E-05	b
9	rs7037324	100658318	9kb 3' of *C9orf156*	A	0.121	0.080	1.56	1.70E-05	b
9	rs72753537	100660746	6kb 3' of *C9orf156*	C	0.030	0.012	1.63	3.56E-06	a
11	rs67790686	103885141	Intronic *PDGFD*	C	0.207	0.153	2.50	3.46E-06	a
12	rs11175834	65992636	132kb 3' of *MSRB3*	T	0.052	0.022	1.45	1.16E-05	e
12	rs16934253	113737225	3'-UTR *SLC24A6*	A	0.203	0.146	2.46	2.49E-09	a
12	rs11061290	131518747	intronic *GPR133*	T	0.134	0.100	1.50	1.41E-06	a
13	rs75150143	52428825	7.3kb 5' of *CCDC70*	C	0.474	0.414	1.40	8.18E-04§	a
14	rs34081947	36559531	208kb 3' of *MBIP*	T	0.511	0.457	1.28	2.40E-04	c
14	rs944289	36649246	119kb 3' of *MBIP*	T	0.464	0.406	1.24	1.41E-03	b
14	rs72693081	81453862	Intronic *TSHR*	G	0.429	0.364	1.27	4.37E-04	d
19	rs7248104	7224431	Intronic *INSR*	A	0.114	0.072	1.31	6.77E-05	d
22	rs7288885	26408660	Intornic *MYO18B*	G	0.112	0.075	1.65	2.42E-06	a

*The SNP positions are indexed to the National Center for Biotechnology Information (NCBI) build 37. ‡SNP selection criteria: a, candidate SNP, significant or suggestive association ($P < 2 \times 10^{-5}$) for our discovery stage; b, previously reported SNPs in GWASs of thyroid cancer; c-e, candidate SNPs, which showed the strongest association in regions reported by GWASs of (c) thyroid cancer and (d) TSH level[11,12] or (e) near gene related to thyroid disease[13,14]. †The *P*-value was calculated after the exclusion of relatedness using IBD. §These SNPs were included because $P < 2 \times 10^{-5}$ before IBD exclusion.

Chr, chromosome number; OR, odd ratio; SNP, single nucleotide polymorphism.

Supplementary Table 4. Comparison of the risk allele frequency between population of 1000 Genome and this study.

Chr	SNP	Gene	Risk / Reference allele	Risk allele frequency in 1000 Genome				Risk allele frequency in this study		
				African	American	European	East Asian	Cases	Controls	Allelic OR
1	rs4915076	*VAV3*	T/C	0.96	0.81	0.93	0.71	0.76	0.70	1.33
1	rs4649295	*PCNXL2*	C/T	0.43	0.75	0.64	0.84	0.87	0.82	1.43
2	rs12990503	*DIRC3*	G/C	0.54	0.35	0.28	0.60	0.69	0.63	1.34
2	rs1549738	*DIRC3*	A/G	0.54	0.84	0.87	0.61	0.58	0.55	1.14
3	rs9858271	*FHIT*	G/A	0.07	0.29	0.24	0.47	0.48	0.43	1.26
4	rs1874564	*SEPT11*	G/A	0.33	0.52	0.45	0.66	0.75	0.69	1.31
8	rs6996585	*NRG1*	G/A	0.24	0.45	0.42	0.23	0.29	0.23	1.39
8	rs12542743	*NRG1*	C/T	0.51	0.56	0.56	0.26	0.32	0.25	1.36
8	rs2439302	*NRG1*	G/C	0.47	0.49	0.48	0.19	0.27	0.21	1.37
9	rs72753537	*FOXE1*	C/T	0.04	0.12	0.14	0.08	0.10	0.07	1.41
12	rs11175834	*MSRB3*	T/C	0.40	0.10	0.05	0.14	0.20	0.15	1.37
12	rs16934253	*SLC24A6*	A/G	0.32	0.08	0.11	0.01	0.03	0.02	1.51
14	rs34081947	*NKX2-1*	T/C	0.20	0.43	0.54	0.39	0.47	0.41	1.27
14	rs944289	*NKX2-1*	T/C	0.15	0.44	0.59	0.45	0.51	0.46	1.25
19	rs7248104	*INSR*	A/G	0.28	0.40	0.42	0.32	0.41	0.36	1.22

Chr, chromosome number; OR, odd ratio; SNP, single nucleotide polymorphism.

Supplementary Table 5. Association between candidate SNPs and *cis*-eQTL results of thyroid tissues in GTEx public data.

Chr	SNP	Position	Representative Gene	RNA-sequencing data in this study			Public data in normal thyroid (source: GTEx2015 v6)	
				Cis-eQTL Gene	*P*-value of tumour tissue	*P*-value of normal tissue	*Cis*-eQTL Gene	*P*-value
1	rs4915076	108359505	*VAV3*	*VAV3*	**0.0174**	0.0995	*VAV3*	**3.33E-27**
							VAV3-AS1	**2.02E-06**
1	rs4649295	233416538	*PCNXL2*	*PCNXL2*	**0.0030**	0.8594	*PCNXL2*	> 0.05
				NTPCR	0.9006	**0.0472**	*NTPCR*	> 0.05
2	rs1549738	218118722	*DIRC3*	*TNS1*	**0.0023**	0.1170	*TNS1*	> 0.05
2	rs12990503	218294217	*DIRC3*	-				
3	rs9858271	59545330	*FHIT*	-				
4	rs1874564	77858105	*SEPT11*	-				
8	rs6996585	32400803	*NRG1*	*NRG1*	**0.0053**	0.0526	*NRG1*	**5.79E-21**
				-			*RP11-1002K11.1*	**6.46E-19**
8	rs12542743	32318355	*NRG1*	*NRG1*	**0.0073**	0.1021	*NRG1*	**2.50E-07**
				-			*RP11-1002K11.1*	**1.00E-06**
8	rs2439302	32432369	*NRG1*	*NRG1*	**0.0025**	**0.0125**	*NRG1*	**6.47E-25**
				-			*RP11-1002K11.1*	**1.76E-23**
9	rs72753537	100660746	*FOXE1*	*C9orf156*	0.6914	0.3035	*C9orf156*	**1.33E-05**
12	rs11175834	65992636	*MSRB3*	-				
12	rs16934253	113737225	*SLC24A6*	-				
14	rs34081947	36559531	*NKX2-1*	*NKX2-1*	**0.0323**	0.5458	*NKX2-1*	> 0.05
				-			*RP11-116N8.4*	**2.90E-12**
				-			*PTCSC3*	**1.50E-05**
14	rs944289	36649246	*NKX2-1*	*NKX2-1*	**0.0069**	**0.0302**	*NKX2-1*	> 0.05
				-			*RP11-116N8.4*	**1.28E-09**
				SFTA3	**0.0107**	**0.0476**	*SFTA3*	> 0.05
19	rs7248104	7224431	*INSR*	-				

The SNP positions are indexed to the National Center for Biotechnology Information (NCBI) build 37. The *cis*-eQTL gene is defined as the genes within ±500 kb the candidate SNP. The *cis*-eQTL result of candidate SNPs are from the association result of 78 tumour thyroid tissues and 23 normal thyroid tissues. The public *cis*-eQTL result of the candidate SNPs are from the GTEx (http://www.gtexportal.org). Bold indicates significance of $P < 0.05$.

Chr, chromosome number; SNP, single nucleotide polymorphism.

Supplementary Table 6. Association between candidate SNPs and the *cis*-eQTL results of various tissues other than thyroid tissue in public data.

Chr	SNP	Position	Representative Gene	Source	eQTL-Gene	Tissue	*P*-value
1	rs4915076	108359505	*VAV3*	Westra2013	*VAV3*	Whole blood	1.56E-08
				GTEx2015_v6	*VAV3*	Lung	3.23E-08
				GTEx2015_v6	*VAV3*	Whole blood	1.91E-06
1	rs4649295	233416538	*PCNXL2*	-	-	-	-
2	rs12990503	218294217	*DIRC3*	GTEx2015_v6	*DIRC3*	Skin	7.19E-06
2	rs1549738	218118722	*DIRC3*	-	-	-	-
3	rs9858271	59545330	*FHIT*	-	-	-	-
4	rs1874564	77858105	*SEPT11*	Westra2013	*CCNI*	Whole blood	0.0013
				Westra2013	*SEPT11*	Whole blood	0.0018
8	rs12542743	32318355	*NRG1*	-			
8	rs6996585	32400803	*NRG1*	Westra2013	*NRG1*	Whole blood	3.95E-190
				GTEx2015_v6	*NRG1*	Whole blood	2.49E-11
				GTEx2015_v6	*RP11-1002K11.1*	Whole blood	7.74E-08
8	rs2439302	32432369	*NRG1*	Westra2013	*NRG1*	Whole blood	9.81E-198
				GTEx2015_v6	*NRG1*	Whole blood	1.68E-13
				GTEx2015_v6	*RP11-1002K11.1*	Whole blood	1.68E-09
9	rs72753537	100660746	*FOXE1*	GTEx2015_v6	*C9orf156*	Adipose	1.15E-05
				GTEx2015_v6	*C9orf156*	Skeletal muscle	3.79E-06
				GTEx2015_v6	*C9orf156*	Nerve, Tibia	5.04E-06
				GTEx2015_v6	*C9orf156*	Testis	1.67E-05
12	rs11175834	65992636	*MSRB3*	-	-	-	-
12	rs16934253	113737225	*SLC24A6*	Westra2013	*AC010178.40-2*	Whole blood	3.50E-04
				Westra2013	*C12orf52*	Whole blood	0.0029
				Westra2013	*SLC24A6*	Whole blood	3.67E-26
14	rs34081947	36559531	*NKX2-1*	GTEx2015_v6	*RP11-116N8.4*	Adipose	2.90E-07
14	rs944289	36649246	*NKX2-1*	GTEx2015_v6	*RP11-116N8.4*	Adipose	5.79E-06
19	rs7248104	7224431	*INSR*	GTEx2015_v6	*INSR*	Nerve, Tibia	2.70E-06

The SNP positions are indexed to the National Center for Biotechnology Information (NCBI) build 37. The *cis*-eQTL result of candidate SNPs are from the GTEx (http://www.gtexportal.org) and Whole blood eQTL (Westra 2013).

Chr, chromosome number; SNP, single nucleotide polymorphism.

Supplementary Table 7. Gene set enrichment analysis results for the candidate SNPs

Chr	SNP	Gene	Normal thyroid tissue		Tumour thyroid tissue		Significant gene set list
			N of gene set (FDR *q*<0.05)	Lowest FDR *q*	*N* of gene set (FDR *q*<0.05)	Lowest FDR *q*	
1	rs4649295	*PCNXL2*	0	0.662	0	0.160	-
1	rs4915076	*VAV3*	0	0.108	**2**	**0.026**	(KEGG) Steroid Hormone Biosynthesis, (Reactome) Steroid Hormones
2	rs12990503	*DIRC3*	0	0.685	**1**	**0.038**	(Reactome) TGF beta receptor signaling activates SMADS
2	rs1549738	*DIRC3*	0	0.267	0	0.200	-
3	rs9858271	*FHIT*	0	0.192	0	0.569	-
4	rs1874564	*SEPT11*	0	0.499	**1**	**0.042**	(Biocarta) ATM Pathway
8	rs12542743	*NRG1*	0	0.234	0	0.860	-
8	rs6996585	*NRG1*	**31**	**< 0.001**	0	0.936	(Biocarta) AT1R Pathway, CXCR4 Pathway, EIF4 Pathway, FCER1 Pathway, FMLP Pathway, GH Pathway, GLEEVEC Pathway, GPCR Pathway, GSK3 Pathway, HCMV Pathway, IGF1 Pathway, IL6 Pathway, Insulin Pathway, MEF2D Pathway, MET Pathway, NFAT Pathway, NFkB Pathway, NGF Pathway, PDGF Pathway, PYK2 Pathway, Stress Pathway, TCR Pathway, VEGF Pathway (KEGG) Axon guidance, Colorectal Cancer (Reactome) Downstream signal trransduction, NGF signalling via TRKA from the plasma membrane, Regulation of KIT signaling, Signaling by FGFR, Signaling by NGF, Transcriptional regulaiton of white adipocyte differntiation
8	rs2439302	*NRG1*	0	0.074	0	0.761	-
9	rs72753537	*FOXE1*	0	0.152	0	0.400	-
12	rs11175834	*MSRB3*	0	0.686	0	0.810	-
12	rs16934253	*SLC24A6*	NA	NA	0	0.997	-
14	rs34081947	*NKX2-1*	0	0.110	0	0.529	-
14	rs944289	*NKX2-1*	0	0.803	0	0.059	-
19	rs7248104	*INSR*	**1**	**0.028**	0	0.650	(Biocarta) ERK Pathway

1077 gene sets (BioCarta, KEGG and Reactome) of Molecular Signatures Database (MSigDB version 5.1) were used. Bold indicates significance of FDR $q < 0.05$.

Chr, chromosome number; FDR *q*, false discovery rate *q*-value; OR, odd ratio; SNP, single nucleotide polymorphism.

Supplementary Table 8. Significantly enriched gene sets (FDR $q < 0.05$) according to the rs6996585 genotype.

Gene set	Description	NES	Nor *P*	FDR *q*
(Biocarta) AT1R Pathway	Angiotensin II mediated activation of JNK Pathway via Pyk2 dependent signaling	2.316	< 0.001	0.001
(Biocarta) PYK2 Pathway	Links between Pyk2 and Map Kinases	2.273	< 0.001	0.004
(Biocarta) IGF1 Pathway	IGF-1 Signaling Pathway	2.108	< 0.001	0.018
(Biocarta) Insulin Pathway	Insulin Signaling Pathway	2.044	< 0.001	0.02
(Biocarta) MET Pathway	Signaling of Hepatocyte Growth Factor Receptor	2.054	< 0.001	0.02
(Reactome) Transcriptional regulation of white adipocyte differentiation	Genes involved in Transcriptional Regulation of White Adipocyte Differentiation	2.124	< 0.001	0.021
(Biocarta) NGF Pathway	Nerve growth factor pathway	2.06	< 0.001	0.022
(Biocarta) GLEEVEC Pathway	Inhibition of Cellular Proliferation by Gleevec	2.084	< 0.001	0.022
(Biocarta) GSK3 Pathway	Inactivation of Gsk3 by AKT causes accumulation of b-catenin in Alveolar Macrophages	2.022	0.002	0.024
(Biocarta) PDGF Pathway	PDGF Signaling Pathway	2.026	< 0.001	0.024
(Biocarta) FCER1 Pathway	Fc Epsilon Receptor I Signaling in Mast Cells	2.002	< 0.001	0.029
(Reactome) NGF signaling via TRKA	Genes involved in NGF signaling via TRKA from the plasma membrane	1.968	< 0.001	0.041
(Biocarta) IL6 Pathway	IL 6 signaling pathway	1.93	< 0.001	0.043
(Biocarta) GPCR Pathway	Signaling Pathway from G-Protein Families	1.931	< 0.001	0.044
(Reactome) Downstream signal transduction	Genes involved in Downstream signal transduction	1.936	< 0.001	0.044
(Biocarta) CXCR4 Pathway	CXCR4 Signaling Pathway	1.95	< 0.001	0.045
(Biocarta) MEF2D Pathway	Role of MEF2D in T-cell Apoptosis	1.938	< 0.001	0.045
(Biocarta) NFkB Pathway	NF-kB Signaling Pathway	1.941	< 0.001	0.046
(KEGG) Colorectal Cancer	Colorectal cancer	1.826	0.002	0.048
(Biocarta) EIF4 Pathway	Regulation of eIF4e and p70 S6 Kinase	1.837	< 0.001	0.048
(Biocarta) HCMV Pathway	Human Cytomegalovirus and Map Kinase Pathways	1.813	0.002	0.048
(KEGG) Axon guidance	Axon guidance	1.839	0.008	0.048
(Biocarta) Stress Pathway	TNF/Stress Related Signaling	1.822	0.008	0.048
(Biocarta) GH Pathway	Growth Hormone Signaling Pathway	1.951	0.008	0.048
(Biocarta) NFAT Pathway	NFAT and Hypertrophy of the heart (Transcription in the broken heart)	1.912	< 0.001	0.049
(Biocarta) TCR Pathway	T Cell Receptor Signaling Pathway	1.837	< 0.001	0.049
(Reactome) Signaling by FGFR	FGFR Signaling pathway	1.816	0.004	0.049
(Reactome) Signaling by NGF	Genes involved in Signaling by NGF	1.839	0.002	0.049
(Biocarta) FMLP Pathway	fMLP induced chemokine gene expression in HMC-1 cells	1.828	0.004	0.049
(Biocarta) VEGF Pathway	VEGF, Hypoxia, and Angiogenesis	1.833	< 0.001	0.049
(Reactome) Regulation of KIT signaling	Genes involved in Regulation of KIT signaling	1.817	0.004	0.049

1077 gene sets (BioCarta, KEGG and Reactome) of Molecular Signatures Database (MSigDB version 5.1) were used.

FDR *q*, false discovery rate *q*-value; NES, normalized enrichment score; Nor *P*, nominal *P*-value.

Supplementary Table 9. Associations between the candidate SNPs and clinical phenotypes.

Chr	SNP	Gene	Clinical phenotype	Genotypes			Total	*P*-value	*BRAF* positive	*BRAF* negative
	rs4915076	*VAV3*		CC	C**T**	**TT**				
			BRAF^{V600E}	10/11(90.9%)	73/83(88.0%)	103/121(85.1%)	186/215(86.5%)	0.477		
			LN metastasis	11/17(64.7%)	71/124(57.3%)	104/196(53.1%)	186/337(55.2%)	0.289	0.855	0.653
			ETE	10/20(50.0%)	78/134(58.2%)	133/223(59.6%)	221/377(58.6%)	0.483	0.634	0.573
1	rs4649295	*PCNXL2*		**CC**	C**T**	TT				
			BRAF^{V600E}	141/162(87.0%)	40/46(87.0%)	4/6(66.7%)	185/214(86.4%)	0.377		
			LN metastasis	145/256(56.6%)	34/72(47.2%)	3/4(75.0%)	182/332(54.8%)	0.356	0.930	0.765
			ETE	169/285(59.3%)	46/80(57.5%)	3/7(42.9%)	218/372(58.6%)	0.489	0.302	0.107
2	rs12990503	*DIRC3*		**CC**	C**G**	GG				
			BRAF^{V600E}	94/105(89.5%)	71/87(81.6%)	20/22(90.9%)	185/214(86.4%)	0.491		
			LN metastasis	94/162(58.0%)	69/137(50.4%)	23/37(62.2%)	186/336(55.4%)	0.763	0.928	0.041
			ETE	108/183(59.0%)	85/153(55.6%)	27/40(67.5%)	220/376(58.5%)	0.669	0.584	0.290
2	rs1549738	*DIRC3*		**AA**	**A**G	GG				
			BRAF^{V600E}	65/74(87.8%)	98/113(86.7%)	21/26(80.8%)	184/213(86.4%)	0.462		
			LN metastasis	65/122(53.3%)	89/161(55.3%)	31/52(59.6%)	185/335(55.2%)	0.459	0.441	0.879
			ETE	82/136(60.3%)	111/184(60.3%)	26/55(47.3%)	219/375(58.4%)	0.187	0.618	0.877
3	rs9858271	*FHIT*		AA	A**G**	**GG**				
			BRAF^{V600E}	35/45(77.8%)	101/111(91.1%)	47/56(83.9%)	183/212(86.3%)	0.478		
			LN metastasis	42/74(56.8%)	98/175(56.0%)	42/82(51.2%)	182/331(55.0%)	0.492	0.328	0.424
			ETE	49/81(60.5%)	114/191(59.7%)	55/99(55.6%)	218/371(58.8%)	0.494	0.934	0.105
4	rs1874564	*SEPT11*		AA	A**G**	**GG**				
			BRAF^{V600E}	11/12(91.7%)	68/76(89.5%)	106/126(84.1%)	185/214(86.4%)	0.236		
			LN metastasis	13/20(65.0%)	67/118(56.8%)	106/196(54.1%)	186/334(55.7%)	0.358	0.229	0.381
			ETE	11/22(50.0%)	75/130(57.7%)	134/223(60.1%)	220/375(58.7%)	0.372	0.688	**0.009**
8	rs12542743	*NRG1*		**CC**	C**T**	TT				
			BRAF^{V600E}	23/27(85.2%)	89/103(86.4%)	72/83(86.7%)	184/213(86.4%)	0.855		
			LN metastasis	27/38(71.1%)	83/155(53.5%)	75/140(53.6%)	185/333(55.6%)	0.156	**0.025**	0.545
			ETE	26/43(60.5%)	110/173(63.6%)	82/157(52.2%)	218/373(58.4%)	0.097	0.152	0.752
8	rs6996585	*NRG1*		AA	A**G**	**GG**				
			BRAF^{V600E}	80/92(87.0%)	81/92(88.0%)	24/29(82.8%)	185/213(86.9%)	0.700		
			LN metastasis	85/153(55.6%)	72/146(49.3%)	26/35(74.3%)	183/334(54.8%)	0.348	**0.015**	0.585
			ETE	96/170(56.5%)	97/166(58.4%)	24/37(64.9%)	217/373(58.2%)	0.393	0.067	0.377
8	rs2439302	*NRG1*		CC	C**G**	**GG**				
			BRAF^{V600E}	84/96(87.5%)	71/85(83.5%)	18/21(85.7%)	173/202(85.6%)	0.589		
			LN metastasis	87/159(54.7%)	65/134(48.5%)	19/23(82.6%)	171/316(54.1%)	0.322	**0.022**	0.908
			ETE	99/175(56.6%)	88/153(57.5%)	17/25(68.0%)	204/353(57.8%)	0.430	0.107	0.376
9	rs72753537	*FOXE1*		**CC**	C**T**	TT				
			BRAF^{V600E}	5/6(83.3%)	44/48(91.7%)	136/160(85.0%)	185/214(86.4%)	0.386		
			LN metastasis	6/8(75.0%)	35/68(51.5%)	145/260(55.8%)	186/336(55.4%)	0.907	0.460	0.636
			ETE	4/9(44.4%)	44/77(57.1%)	173/290(59.7%)	221/376(58.8%)	0.392	0.566	0.212
12	rs11175834	*MSRB3*		CC	C**T**	**TT**				
			BRAF^{V600E}	116/132(87.9%)	56/67(83.6%)	10/12(83.3%)	182/211(86.3%)	0.392		
			LN metastasis	123/218(56.4%)	48/95(50.5%)	11/18(61.1%)	182/331(55.0%)	0.691	0.403	0.746
			ETE	145/242(59.9%)	61/108(56.5%)	10/18(55.6%)	216/368(58.7%)	0.506	0.600	0.533
12	rs16934253	*SLC24A6*		**AA**	**A**G	GG				
			BRAF^{V600E}	0/0 (0%)	22/25(88.0%)	164/190(86.3%)	186/215(86.5%)	0.822		
			LN metastasis	0/0 (0%)	17/37(45.9%)	169/300(56.3%)	186/337(55.2%)	0.245	0.064	0.127
			ETE	0/0 (0%)	23/39(59.0%)	198/338(58.6%)	221/377(58.6%)	0.963	0.592	0.392
14	rs34081947	*NKX2-1*		CC	C**T**	**TT**				
			BRAF^{V600E}	59/63(93.7%)	91/107(85.0%)	35/43(81.4%)	185/213(86.9%)	0.056		
			LN metastasis	50/92(54.3%)	94/172(54.7%)	42/72(58.3%)	186/336(55.4%)	0.633	0.509	0.726
			ETE	58/102(56.9%)	119/193(61.7%)	43/80(53.8%)	220/375(58.7%)	0.756	0.945	0.836
14	rs944289	*NKX2-1*		CC	C**T**	**TT**				
			BRAF^{V600E}	52/58(89.7%)	89/104(85.6%)	45/53(84.9%)	186/215(86.5%)	0.450		
			LN metastasis	43/84(51.2%)	91/167(54.5%)	52/86(60.5%)	186/337(55.2%)	0.221	0.206	0.634
			ETE	53/92(57.6%)	112/192(58.3%)	56/93(60.2%)	221/377(58.6%)	0.721	0.338	0.758
19	rs7248104	*INSR*		**AA**	**A**G	GG				
			BRAF^{V600E}	34/39(87.2%)	86/98(87.8%)	60/71(84.5%)	180/208(86.5%)	0.623		

	LN metastasis	30/57(52.6%)	87/164(53.0%)	63/108(58.3%)	180/329(54.7%)	0.419	0.355	0.156
	ETE	49/70(70.0%)	107/181(59.1%)	59/116(50.9%)	215/367(58.6%)	**0.010**	0.571	**0.001**

All analyses were conducted with papillary thyroid cancer. Bold genotype indicates risk allele. Bold *P*-value indicates significance of < 0.05.
Chr, chromosome number; ETE, extrathyroidal extension; LN, lymph node; OR, odd ratio; SNP, single nucleotide polymorphism.

Supplementary Table 10. SNPs in the *FOXE1* region and DTC and PTC associations in a Korean population.

Chr	SNP	Position	Gene	Risk Allele	Stage	DTC			PTC		
						Allele Frequency (case/control)	OR	*P*	Allele Frequency (case/control)	OR	*P*
9	rs965513	100556109	*FOXE1*	A	Discovery	0.11/0.06	1.91	2.35E-09	0.11/0.06	1.94	8.20E-09
					Replication	0.09/0.07	1.25	0.1372	0.09/0.07	1.23	0.1653
					Joint	0.10/0.06	1.67	6.20E-11	0.10/0.06	1.66	4.48E-10
9	rs1588635	100537802	*FOXE1*	A	Discovery	0.11/0.07	1.81	1.74E-08	0.12/0.07	1.83	6.76E-08
					Replication	0.09/0.08	1.18	0.2425	0.09/0.08	1.17	0.2706
					Joint	0.10/0.07	1.58	2.36E-09	0.10/0.07	1.57	1.30E-08
9	rs7028661	100538470	*FOXE1*	A	Discovery	0.11/0.07	1.80	2.52E-08	0.12/0.07	1.82	9.47E-08
					Replication	0.09/0.08	1.20	0.2090	0.09/0.08	1.19	0.2343
					Joint	0.10/0.07	1.57	3.08E-09	0.10/0.07	1.56	1.64E-08
9	rs10122541	100628268	*FOXE1*	G	Discovery	0.12/0.08	1.57	1.43E-05	0.10/0.06	1.81	4.07E-07
					Replication	0.10/0.08	1.22	0.1690	0.08/0.07	1.03	0.8341
					Joint	0.11/0.08	1.36	4.25E-06	0.09/0.06	1.48	4.77E-06
9	rs72753537	100660746	*FOXE1*	C	Discovery	0.12/0.07	1.63	3.56E-06	0.12/0.07	1.76	1.70E-07
					Replication	0.09/0.07	1.38	**0.0352**	0.09/0.07	1.43	**0.0209**
					Joint	0.10/0.07	1.41	7.67E-06	0.11/0.07	1.48	5.37E-07
9	rs7037324	100658318	*FOXE1*	A	Discovery	0.12/0.08	1.56	1.70E-05	0.19/0.13	1.56	1.43E-06
					Replication	0.10/0.08	1.28	0.0865	0.15/0.14	1.11	0.3758
					Joint	0.11/0.08	1.38	1.28E-05	0.17/0.13	1.32	1.62E-05
9	rs1867277	100615914	*FOXE1*	A	Discovery	0.17/0.12	1.44	4.38E-05	0.18/0.12	1.54	4.96E-06
					Replication	0.12/0.13	0.89	0.3109	0.11/0.13	0.86	0.1982
					Joint	0.14/0.12	1.18	0.0176	0.15/0.12	1.19	0.0146

The SNP positions are indexed to the National Center for Biotechnology Information (NCBI) build 37. Bold indicates significance of $P < 0.05$ in replication stage.

Chr, chromosome number; OR, odd ratio; SNP, single nucleotide polymorphism.

Supplementary Table 11. A comparison of previously reported SNPs associated with DTC or PTC in Europeans and Koreans.

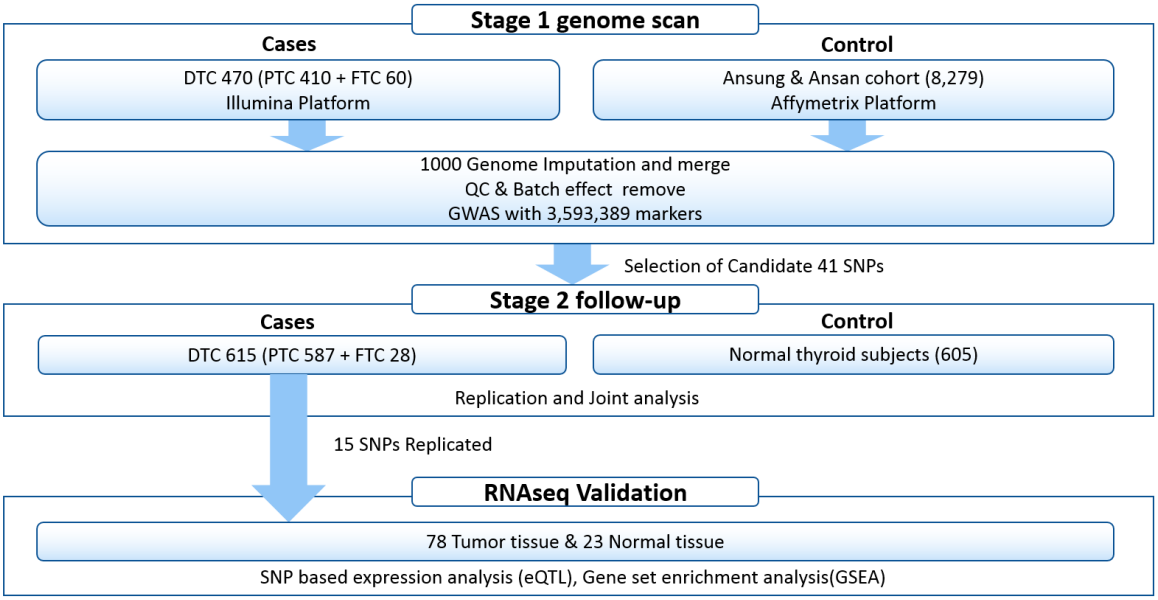
Gene	SNP	Europeans			DTC in Koreans		PTC in Koreans	
		OR	*P*-value	population	OR	*P*-value	OR	*P*-value
FOXE1	rs965513	1.75	1.7×10^{-27}	Iceland etc.	1.91	2.4×10^{-9}	1.94	8.2×10^{-9}
FOXE1	rs7028661	1.64	1.0×10^{-22}	Spain	1.80	2.5×10^{-8}	1.82	9.5×10^{-8}
FOXE1	rs10122541	1.54	1.1×10^{-17}	Spain	1.57	1.4×10^{-5}	1.69	1.2×10^{-6}
FOXE1	rs7037324	1.54	1.2×10^{-17}	Spain	1.56	1.7×10^{-5}	1.68	1.4×10^{-6}
NRG1	rs2439302	1.36	2.0×10^{-9}	Iceland etc.	1.34	8.4×10^{-5}	1.48	1.5×10^{-6}
NKX2-1	rs944289	1.37	2.0×10^{-9}	Iceland etc.	1.24	0.0014	1.22	0.0062
DIRC3	rs966423	1.34	1.3×10^{-9}	Iceland etc.	1.24	0.0081	1.27	0.0067
DIRC3	rs6759952	1.21	6.4×10^{-10}	Italy etc.	1.21	0.0164	1.25	0.0107
IMMP2L	rs10238549	1.27	4.1×10^{-6}	Italy etc.	1.10	0.3542	1.17	0.1343
IMMP2L	rs7800391	1.25	5.7×10^{-6}	Italy etc.	1.03	0.7271	1.00	0.9850
DHX35	rs7267944	1.39	2.1×10^{-8}	Italy etc.	0.98	0.8209	0.98	0.7752
ARSB	rs13184587	1.28	8.5×10^{-6}	Italy etc.	1.03	0.7453	1.02	0.8216
WDR11-AS1	rs2997312	1.35	1.2×10^{-4}	Spain	0.94	0.6299	0.97	0.8039
WDR11-AS1	rs10788123	1.26	5.2×10^{-4}	Spain	0.92	0.2401	0.94	0.4540

OR, odd ratio; SNP, single nucleotide polymorphism.

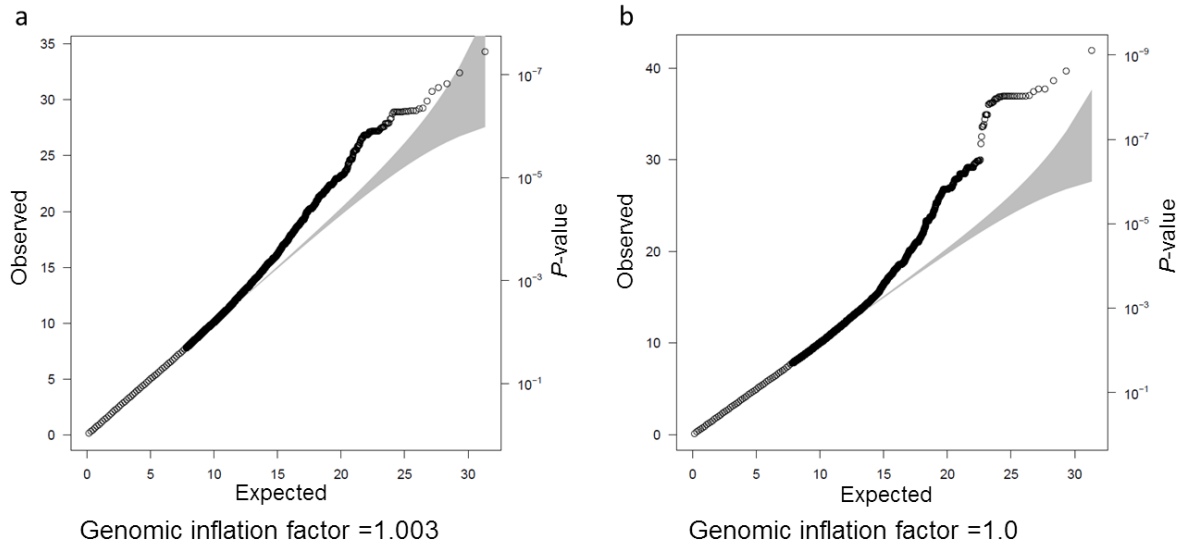
Supplementary Table 12. Variants of six recently reported novel and replicating loci for thyroid cancer in a Korean population.

Locus	SNP	Position	Annotation/ Nearby gene(s)	*P*-value of Gudmundsson et al.	Discovery result in this study		
					P-value	Nearby top SNP with $P < 0.001$	*P*-value (Joint *P*) of nearby top SNP
1q42.2	rs12129938	233,276,815	Intron variant *PCNXL2*	4.0E-11	0.002	rs4649295	1.04E-05 (6.00E-08)
10q24.33	rs7902587	103,934,543	Intergenic variant *OBFC1*	5.4E-11	NA	rs4244255	8.72E-06
5q22.1	rs73227498	112,150,207	Intergenic variant *NREP, EPB41L4A*	3.0E-10	NA	-	
15q22.33	rs2289261	67,165,147	Intron variant *SMAD3*	3.1E-9	0.2844	-	
3q26.2	rs6793295	169,800,667	Missense variant *TERC, LRRC34*	2.7E-8	0.0474	-	
5p15.33	rs10069690	1,279,675	Intron variant *TERT*	3.2E-7	NA	-	

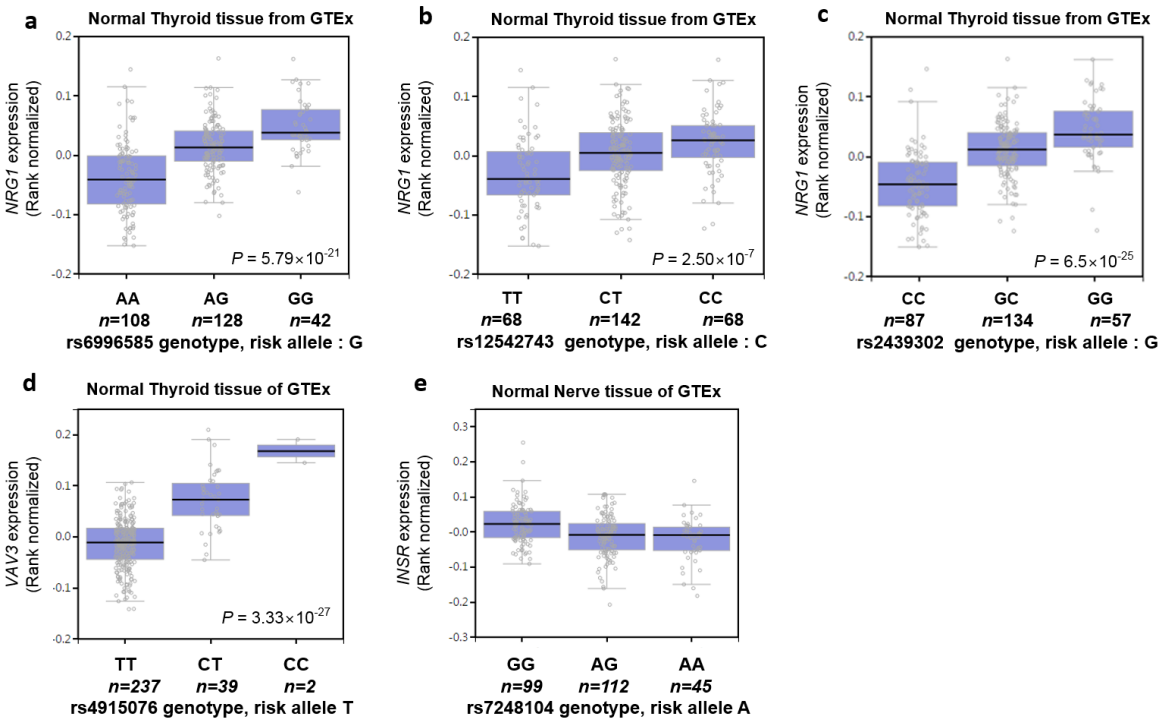
NA, not available; SNP, single nucleotide polymorphism.



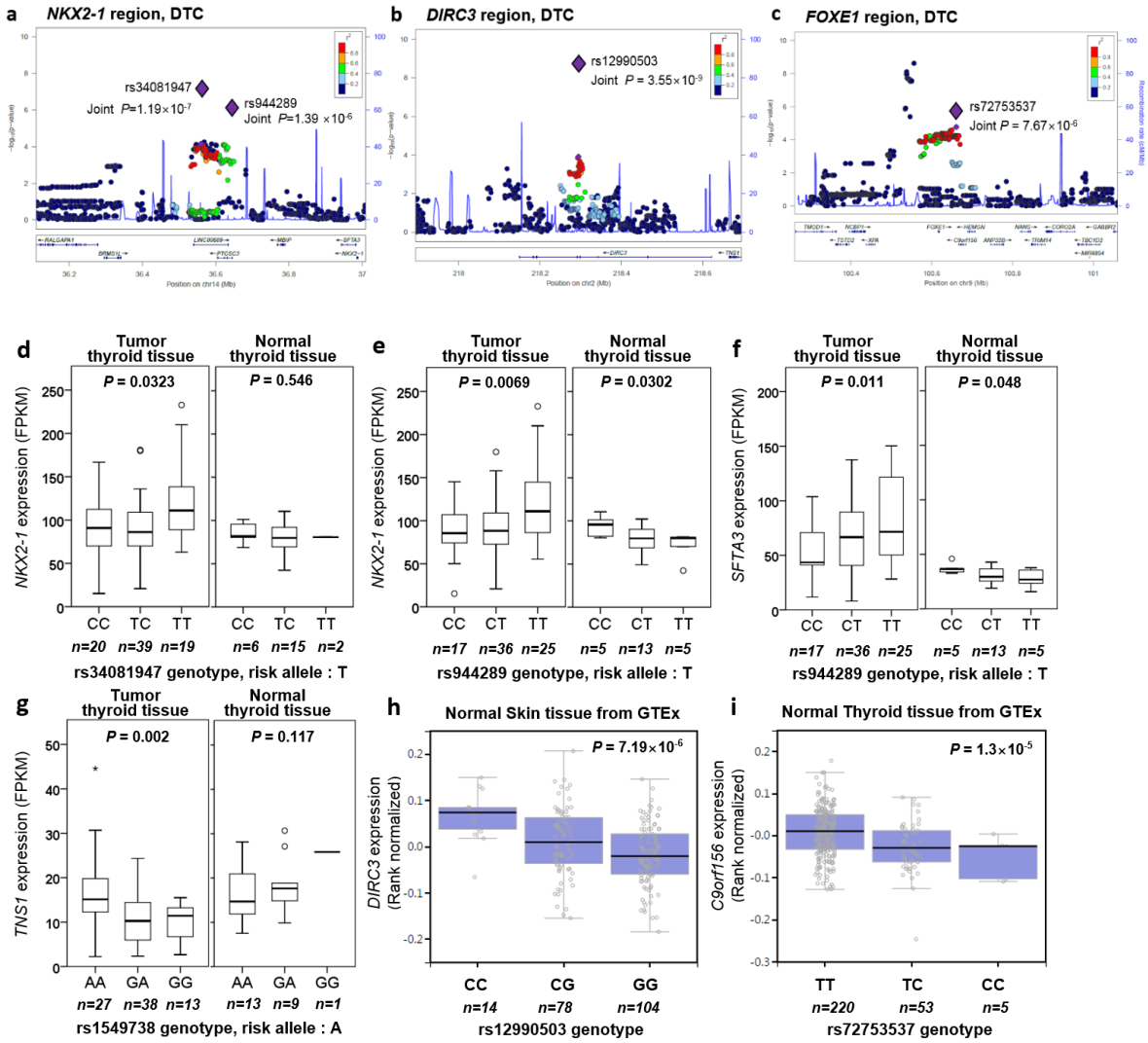
Supplementary Figure 1. Overview of the study flow. The number of individuals with DTC (PTC + FTC) or unaffected individual; the imputed or replicated genotypes are shown for each study flow.



Supplementary Figure 2. Quantile-quantile plot for stage 1 genome scans. A quantile-quantile plot for (a) DTC and (b) PTC showing the distribution of the observed *P*-values from association testing in the stage 1 genome scan against the expected distribution under the null hypothesis. The grey zone indicates the 95% confidence interval.



Supplementary Figure 3. *Cis*-eQTL results from GTEx public data. The *cis*-eQTL results of *NRG1* in normal thyroid tissue according to the (a) rs6996585, (b) rs12542743 and (c) rs2439302 genotypes. The *cis*-eQTL results of (d) *VAV3* in normal thyroid tissue according to the rs4915076 genotype and (e) *INSR* in normal nerve tissue according to the rs7248104 genotype from GTEx2015 v6 data (http://www.gtexportal.org).



Supplementary Figure 4. Regional association plots and expression for previously documented loci. A regional association plot for (a) *NKX2-1*, (b) *DIRC3* and (c) *FOXE1*. The large purple diamonds indicate the most or second most associated SNP according to joint analyses and nearby SNPs are colour coded according to the level of LD with the top SNP. The left y-axis shows the significance of the association on a $-\log_{10}$ scale, and the right y-axis shows a recombination rate across the region. Estimated recombination rates from the 1000 Genomes ASN, hg19 database are plotted with the blue line to reflect the local LD structure. The *cis*-eQTL results of *NKX2-1* according to the (d) rs34081947 and (e) rs944289 genotypes; (f) *SFTA3* according to the rs944289 genotypes; and (g) *TNS1* according to the rs1549738 genotypes in tumour and normal thyroid tissues. Error bars represent s.e.m. The *cis*-eQTL results of (h) *DIRC3* in skin tissue and (i) *C9orf156* in thyroid tissue from GTEx2015 v6 data (http://www.gtexportal.org) according to the rs12990503 and rs72753537 genotypes, respectively.

Supplementary Reference

1. Gudmundsson, J. *et al.* Common variants on 9q22.33 and 14q13.3 predispose to thyroid cancer in European populations. *Nat Genet* **41**, 460-4 (2009).
2. Takahashi, M. *et al.* The FOXE1 locus is a major genetic determinant for radiation-related thyroid carcinoma in Chernobyl. *Hum Mol Genet* **19**, 2516-23 (2010).
3. Matsuse, M. *et al.* The FOXE1 and NKX2-1 loci are associated with susceptibility to papillary thyroid carcinoma in the Japanese population. *J Med Genet* **48**, 645-8 (2011).
4. Wang, Y.L. *et al.* Confirmation of papillary thyroid cancer susceptibility loci identified by genome-wide association studies of chromosomes 14q13, 9q22, 2q35 and 8p12 in a Chinese population. *J Med Genet* **50**, 689-95 (2013).
5. Rogounovitch, T.I. *et al.* The common genetic variant rs944289 on chromosome 14q13.3 associates with risk of both malignant and benign thyroid tumors in the Japanese population. *Thyroid* **25**, 333-40 (2015).
6. Mancikova, V. *et al.* Thyroid cancer GWAS identifies 10q26.12 and 6q14.1 as novel susceptibility loci and reveals genetic heterogeneity among populations. *Int J Cancer* **137**, 1870-8 (2015).
7. Gudmundsson, J. *et al.* Discovery of common variants associated with low TSH levels and thyroid cancer risk. *Nat Genet* **44**, 319-22 (2012).
8. Kohler, A. *et al.* Genome-wide association study on differentiated thyroid cancer. *J Clin Endocrinol Metab* **98**, E1674-81 (2013).
9. Figlioli, G. *et al.* Novel genome-wide association study-based candidate loci for differentiated thyroid cancer risk. *J Clin Endocrinol Metab* **99**, E2084-92 (2014).
10. Figlioli, G. *et al.* Novel genetic variants in differentiated thyroid cancer and assessment of the cumulative risk. *Sci Rep* **5**, 8922 (2015).
11. He, H. *et al.* Genetic predisposition to papillary thyroid carcinoma: involvement of FOXE1, TSHR, and a novel lincRNA gene, PTCSC2. *J Clin Endocrinol Metab* **100**, E164-72 (2015).
12. Porcu, E. *et al.* A meta-analysis of thyroid-related traits reveals novel loci and gender-specific differences in the regulation of thyroid function. *PLoS Genet* **9**, e1003266 (2013).
13. Kucharzewski, M., Braziewicz, J., Majewska, U. & Gozdz, S. Concentration of selenium in the whole blood and the thyroid tissue of patients with various thyroid diseases. *Biol Trace Elem Res* **88**, 25-30 (2002).
14. Kim, H.Y. The methionine sulfoxide reduction system: selenium utilization and methionine sulfoxide reductase enzymes and their functions. *Antioxid Redox Signal* **19**, 958-69 (2013).