

# A Comprehensive Meta-analysis of Case-Control Association Studies to Evaluate Polymorphisms Associated with the Risk of Differentiated Thyroid Carcinoma

Gisella Figlioli<sup>1,2</sup>, Rossella Elisei<sup>3</sup>, Cristina Romei<sup>3</sup>, Ombretta Melaiu<sup>2</sup>, Monica Cipollini<sup>2</sup>, Franco Bambi<sup>4</sup>, Bowang Chen<sup>1</sup>, Aleksandra Köhler<sup>1,5</sup>, Alfonso Cristaudo<sup>3</sup>, Kari Hemminki<sup>1,6</sup>, Federica Gemignani<sup>2</sup>, Asta Försti<sup>1,6</sup>, and Stefano Landi<sup>2</sup>

## Abstract

**Background:** Linkage analyses and association studies suggested that inherited genetic variations play a role in the development of differentiated thyroid carcinoma (DTC).

**Methods:** We combined the results from a genome-wide association study (GWAS) performed by our group and from published studies on DTC. With a first approach, we evaluated whether a SNP published as associated with the risk of DTC could replicate in our GWAS (using FDR as adjustment for multiple comparisons). With the second approach, meta-analyses were performed between literature and GWAS when both sources suggested an association, increasing the statistical power of the analysis.

**Results:** rs1799814 (*CYP1A1*), rs1121980 (*FTO*), and 3 SNPs within 9q22 (rs965513, rs7048394, and rs894673)

replicated the associations described in the literature. In addition, the meta-analyses between literature and GWAS revealed 10 more SNPs within 9q22, six within *FTO*, two within *SOD1*, and single variations within *HUS1*, *WDR3*, *UGT2B7*, *ALOX12*, *TICAM1*, *ATG16L1*, *HDAC4*, *PIK3CA*, *SULF1*, *IL11RA*, *VEGFA*, and 1p31.3, 2q35, 8p12, and 14q13.

**Conclusion:** This analysis confirmed several published risk loci that could be involved in DTC predisposition.

**Impact:** These findings provide evidence for the role of germline variants in DTC etiology and are consistent with a polygenic model of the disease. *Cancer Epidemiol Biomarkers Prev*; 25(4): 700–13. ©2016 AACR.

## Introduction

Thyroid carcinoma is the most common malignancy of the endocrine system showing increasing incidences over the years (1–3), with age-standardized rates (ASR) of about 6/100,000 in the developed countries. Particularly elevated ASRs were observed in Lithuania (ASR = 15.5/100,000), Italy (ASR =

13.5/100,000), Austria (ASR = 12.4/100,000), and in the United States (ASR = 9.9/100,000; refs. 4, 5). Two main thyroid carcinoma histological types can be distinguished: the "medullary" and the "non-medullary" thyroid carcinoma, the former (MTC) originating from the para-follicular cells, the latter (NMTC) from the follicular cells. NMTC comprises the most frequent subtypes, papillary (PTC) and follicular (FTC) thyroid carcinomas (defined overall as "differentiated thyroid carcinomas", DTC), accounting for 80% and 15% of the cases, respectively. Hürthle cells (or oxyphilic cells, 5%) and poorly differentiated carcinomas (1%–6%) are considered as not common entities (6, 7).

The great majority of DTCs behaves as a sporadic form, featured by somatic mutations within *RET*, *RAS*, *BRAF*, or *NTRK1* genes and affecting the MAPK signaling pathway (8–11). However, approximately 5% of cases, mostly PTC, have a family history (12). Inherited genetic variations play an important role in both the familial and the sporadic forms, as supported by data from linkage analyses or case-control association studies (CCASs). In particular, CCASs, when carried out with an appropriate sample size, constitute the state-of-the-art for the identification of common genetic variants associated with complex traits (13). In the literature, a large number of gene-based studies have been published in which specific *a priori* hypotheses have been examined. Thus, SNPs within genes encoding for proteins involved in the DNA repair, cell-cycle control, thyroid physiology,

<sup>1</sup>Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany. <sup>2</sup>Department of Biology, University of Pisa, Pisa, Italy. <sup>3</sup>Department of Endocrinology and Metabolism, University of Pisa, Pisa, Italy. <sup>4</sup>Blood Centre, Azienda Ospedaliero Universitaria A. Meyer, Firenze, Italy. <sup>5</sup>II Medizinische Klinik, Gastrologie, Onkologie und Palliativmedizin, St. Agnes-Hospital Bochohl, Bochohl, Germany. <sup>6</sup>Center for Primary Health Care Research, Clinical Research Center, Lund University, Malmö, Sweden.

**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

F. Gemignani, A. Försti, and S. Landi contributed equally to this article.

**Corresponding Authors:** Stefano Landi, Department of Biology, University of Pisa, Via Derna 1, 56126 Pisa, Italy. Phone: 39-0502211529; Fax: 39-0502211527; E-mail: stefano.landi@unipi.it; and Asta Försti, Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, 69120 Heidelberg, Germany. Phone: 49-6221421803; Fax: 49-6221421810; E-mail: a.foersti@dkfz-heidelberg.de

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or playing a role in other types of human cancer have been investigated (14). The major weakness of these studies is that unknown genes playing a relevant role in the etiology of the disease could have been missed. This limitation is solved by genome-wide association studies (GWASs) in which the whole genome is analyzed without formulating any *a priori* hypothesis. GWASs on DTC allowed discovering novel variants, including those near *FOXEL1*, *DIRC3*, *NKX2-1* (15–17) and, more recently, those near *IMMP2L*, *RARRES1*, *SNAPC4/CARD9*, *ARSB*, *BATF*, *DHX35*, *SPATA13*, *GALNTL4*, and *FOXA2* (18–20). However, to ensure a high quality and to prevent false-positive findings, highly stringent criteria are applied in the GWASs with the disadvantage of excluding SNPs truly associated with the risk. In the present work, we investigated whether SNPs associated with the susceptibility to DTC in previous CCASs could replicate in an independent GWAS carried out by our research group. Moreover, we investigated whether SNPs showing a sub-threshold genome-wide statistical significance in our GWAS could improve their association following a meta-analysis with previously published data.

## Materials and Methods

### Ethics statement

Study participants were recruited according to the protocols approved by the institutional review boards in accordance with the Declaration of Helsinki. All subjects provided written informed consent to participate in the study and allowed the use of their biological samples.

### Study participants of the GWAS

The group of cases comprised 701 histologically confirmed DTC patients from central and southern Italy, recruited at the Cisanello Hospital in Pisa, an important Italian referral center for thyroid diseases. The control group comprised 499 healthy individuals from the Meyer Hospital in Florence without known thyroid disease, of which 390 were blood donor volunteers and 109 were healthy individuals recruited during a routine health screening. Cases and controls were frequency matched by sex, age, body mass index (BMI), and smoking habits. The patient group consisted of 22.3% males and 77.7% females with a median age of 46; the control group consisted of 23.2% males and 76.8% females with a median age of 50. The median BMI was 24.5 in cases and 24.4 in controls. The proportion of smokers was 37% in cases and 40% in controls. All cases and controls were of Caucasian origin.

### Genome-wide association study

Full details of the GWAS, including the genotyping process, quality control and statistical analysis were previously described (20). Briefly, samples were genotyped using Illumina HumanOmni1-Quad\_v1-0\_B 1M BeadChips and Illumina HumanOmniExpress-12v1\_A 730K BeadChips. Genotype calling was performed using Illumina GenomeStudio 2010 (Illumina Inc.). After applying strict quality control criteria, the analysis was restricted to the subset of genotyped SNPs common to both Illumina arrays used. Hence, 572 042 SNPs were analyzed for association with DTC risk in 690 cases and 497 controls. The adequacy of the case–control matching and the possibility of differential genotyping of cases and controls were assessed using Q-Q plots of test statistics. The genomic control

inflation factor  $\lambda$  was calculated using the standard method by the CRAN R package GAP (Genetic Analysis Package; <https://cran.r-project.org/web/packages/gap/index.html>; <http://www.inside-r.org/packages/cran/gap/docs/gcontrol2>).

The inflation factor  $\lambda$  was 1.0, excluding the possibility of hidden population substructure, relatedness among subjects or differential genotype calling. Statistical analysis was conducted using PLINK version 1.06 (21).

### Search strategy and selection criteria

PubMed was searched from database inception until September 2013 to collect case–control studies investigating the association between SNPs and DTC. We used the keywords *polymorph\** AND (*papillary OR follicular OR non-medullary OR "non medullary"*) AND *thyroid* AND (*cancer OR carcinoma*) AND (*susceptibility OR risk OR predisposition*) to collect studies carried out on DTC or PTC. The major reasons for exclusion of the studies were (i) studies not in English language; (ii) studies without odds ratio (OR) and 95% confidence interval (95% CI); (iii) case–case studies; (iv) studies on benign thyroid disease. A total of 100 original articles and five meta-analyses met our criteria and were assessed. The list of citations is reported, for brevity, in the Supplementary data. The SNPs reported in these studies were recorded and searched in the present GWAS, allowing a direct comparison between the results published in the literature with the results from the GWAS. When an SNP was not found in the GWAS, the linkage disequilibrium (LD) block around the SNP was checked using the CEU data of the 1000 Genome Project (22), and the results of SNPs in high LD ( $r^2 \geq 0.8$ ) were reported. All the collected data are reported in Supplementary Tables S1 and S2.

### Statistical approaches

Two statistical approaches were used to reduce the number of false positives and to increase the power of the study. With the first approach, we performed a meta-analysis of published data when more than one study was carried out on a given SNP. Then, we evaluated whether SNPs previously associated with the risk of DTC (positive, at a nominal significance level of  $P_{\text{ass}} < 0.05$ , either in a single study or in meta-analysis) were associated also with the risk of DTC in our GWAS. These SNPs were evaluated by calculating their allelic  $P_{\text{ass}}$  in the GWAS. In order to adjust for multiple comparisons, the false-positive discovery rate correction (FDR; ref. 23) was applied to the list of  $P_{\text{ass}}$  obtained in the GWAS and the associations with  $q < 0.05$  were considered as statistically significant, i.e., considered as replicating the literature data.

With the second approach, results from SNPs positive in the literature (either in a single study or in the meta-analysis of the literature) were meta-analyzed with those of GWAS. Moreover, the meta-analyses were performed also when, for a given SNP, a suggestive evidence of association ( $P_{\text{ass}} < 0.20$ , taken arbitrarily) was observed both in the literature and in the GWAS. Because the GWAS was performed on Caucasians, the meta-analysis first was carried out in Caucasians. When literature data were not available for Caucasians, the GWAS was meta-analyzed using literature data for the available population(s).

The pooled ORs were calculated for allelic model (a vs. A) and additive model (Aa vs. AA and aa vs. AA). In case only dominant or recessive model was reported in the literature, the same model was applied for the GWAS data.

The statistics are based on the absolute counts of variant and common alleles/genotypes among cases and controls. The  $\chi^2$  based Q-test was used to assess heterogeneity across studies ( $P_{\text{het}} < 0.05$ ) and  $I^2$  statistics was calculated to quantify the proportion of the total variation across studies due to heterogeneity. In case of no significant heterogeneity, OR and 95% CI were assessed using the fixed-effect model (the Mantel–Haenszel method); otherwise the random-effects model (DerSimonian–Laird method) was used. Meta-analyses were performed by MIX 1.7 freeware software. Also in this case, adjustment for multiple comparisons was performed by applying the FDR correction and  $q < 0.05$  were considered as significant. A SNP associated with the risk of DTC in the literature was considered replicated when found with a  $q < 0.05$  also in the GWAS. Moreover, an SNP was considered positively associated with the risk of DTC when found with a  $q < 0.05$  in the meta-analysis.

## Results

One hundred published articles, reporting results for 316 SNPs belonging to 127 genes, met the selection criteria (see the reference list in the Supplementary data). Data collected included the reference of the literature, the gene name, the dbSNP identification number, the number of cases and controls investigated, and the OR with its 95% CI, of the allelic and additive models. In the first type of evaluation, the corresponding ORs and 95% CIs were also calculated for these SNPs based on the GWAS. In case only dominant or recessive model was reported in the literature, the same model was applied for the GWAS data. The results are reported side-by-side in Supplementary Tables S1 and S2, respectively, to allow a direct comparison. Among the 316 SNPs, 91 were associated with the risk of DTC in a statistically significant way according to the literature ( $P_{\text{ass}} < 0.05$ ). The meta-analysis of the literature data alone was performed on 46 SNPs and 13 were statistically significant at the 0.05 level (Supplementary Table S3). Fifteen of the 91 SNPs associated in any study were replicated in the GWAS at the same significance level, and the side-by-side comparison is shown in Table 1. However, only five SNPs, including *CYP1A1* rs1799814, *FTO* rs1121980, and the GWAS identified SNPs on 9q22 (rs965513, rs7048394, and rs894673), were statistically significant after the application of FDR correction. Only one SNP (rs965513) showed to be associated in a statistically significant way in the meta-analysis of literature data and in the present GWAS (Table 1). In addition to these analyses, we adopted another approach. In order to ascertain whether an increase of statistical power could allow reaching a statistical significance, we selected SNPs showing a  $P_{\text{ass}} < 0.2$  (arbitrarily chosen, in any inheritance model) both in the literature and in the GWAS and we performed a meta-analysis. Moreover, we added the results of the present GWAS to meta-analyses from literature data, when these latter showed SNPs significantly associated with the risk of DTC.

Results from the meta-analyses are shown in Tables 2 and 3. Below, we summarize the results according to the biological processes.

### SNPs within DNA repair genes

A total of 64 SNPs located within 27 genes involved in DNA repair pathways were investigated so far in the context of DTC. Of them, 10 were associated with the disease in the literature with at least one genetic model but none was replicated in the present GWAS under the allelic model (Table 1). However, a statistical significance was observed for rs25487 within *XRCC1* (OR = 0.76, 95% CI, 0.59–0.99 for heterozygotes in the additive model). When this result was combined in meta-analysis with seven previous studies carried out on Caucasians, an OR of 0.92 (95% CI, 0.85–0.99) was found in the allelic model; however, this result was not significant after FDR correction ( $q = 0.06$ ). Moreover, the meta-analyses revealed an increased risk for rs2708906, at 5' region near *HUS1* (OR = 1.34; 95% CI, 1.08–1.64;  $q = 0.04$  for heterozygotes and OR = 1.52; 95% CI, 1.16–2.00;  $q = 0.01$  for homozygotes; Table 2).

### SNPs within cell-cycle regulation and apoptosis genes

Thirty-three common SNPs in 15 genes involved in the cell-cycle regulation or in apoptosis were collected. A total of nine significance associations were published so far, but only rs4658973 (*WDR3*) was replicated in the GWAS (allelic model: OR = 0.83; 95% CI, 0.70–1.00). Meta-analysis on Caucasians again suggested the role of this variant in DTC etiology with OR = 0.71 (95% CI, 0.61–0.82, allelic model), remaining significant after FDR correction ( $q = 1.8 \times 10^{-6}$ ; Tables 1 and 2). Moreover, when the GWAS association on Caucasians was combined with a mixed population from a previous study, a statistical significance was found for rs2279744 (*MDM2*, OR = 1.40, 95% CI, 1.12–1.74; only recessive model was available for meta-analysis; Table 3).

### SNPs within genes encoding for xenobiotic metabolism enzymes

Through PubMed search, 67 SNPs within 19 genes encoding for xenobiotic metabolism enzymes (XME) were collected. Overall, 19 positive associations were reported in the literature. Interestingly, rs1799814 (*CYP1A1*) showed a strong association in GWAS and it remained statistically significant after FDR correction (Table 1). In the meta-analysis, a high risk was found associated with the rare allele (OR = 1.86, 95% CI, 1.50–2.30,  $q = 4.4 \times 10^{-8}$ ). Besides rs1799814, meta-analyses on Caucasians, after multiple testing correction, revealed a possible role also for rs1041740 (*SOD1*,  $q = 5.5 \times 10^{-3}$ ; allelic model), rs12626475 (3' region near *SOD1*,  $q = 0.02$ ; allelic model), and rs3924194 (*UGT2B7*,  $q = 0.04$ ; for heterozygotes; Table 2).

### SNPs within genes involved in thyroid function

Seven genes playing a key role in thyroid function were assessed in DTC studies by genotyping 21 SNPs. Only five SNPs were reported as significantly associated with DTC, and none of them was significant in the GWAS. Thus, the meta-analyses did not confirm the role of these variants in DTC etiology (Tables 1 and 2).

### SNPs within MAPK pathway genes

Of 17 SNPs within 8 genes of the MAPK pathway, four predisposing variants were reported. GWAS replicated the significant association found for rs12628 (*HRAS*, OR = 1.23,

**Table 1.** List of SNPs associated with the risk of DTC in previous studies published in the literature

Gene or locus	dbSNP ID; variant	Author, year	Literature best $P_{\text{ass}}$	Meta-analysis of the literature	GWAS allelic $P_{\text{ass}}$	GWAS allelic $q$
DNA repair						
<i>ALKBH3</i>	rs10838192	Neta et al. 2011 (25)	$9.42 \times 10^{-4}$	—	0.79	0.92
<i>BRCA1</i>	rs799917	Xu et al. 2012 (26)	0.04	0.07	0.69	0.92
<i>BRIP1</i>	rs2048718; -1918G>A	Sigurdson et al. 2009 (27)	0.01	—	0.21	0.70
<i>HUS1</i>	rs2708906	Neta et al. 2011 (25)	$2.18 \times 10^{-4}$	—	0.26	0.70
<i>RAD52</i>	rs11226; *744C>T	Siraj et al. 2008 (28)	$8.52 \times 10^{-4}$	—	0.87	0.95
<i>XRCC1</i>	rs1799782; Arg194Trp	Chiang et al. 2008 (29)	0.02	0.63	0.64	0.92
<i>XRCC1</i>	rs25489	García-Qu. et al. 2011 (30)	0.03	0.73	0.24	0.70
<i>XRCC1</i>	rs25487	Ho et al. 2009 (31)	0.01	0.24	0.13	0.53
<i>XRCC3</i>	rs861539; Thr241Met	Sturgis et al. 2005 (32)	$2.48 \times 10^{-3}$	0.13	0.34	0.74
<i>XRCC7</i>	rs7830743	Rahimi et al. 2012 (33)	$1.17 \times 10^{-4}$	0.01	0.66	0.92
Cell-cycle regulation and apoptosis						
<i>BAK1</i>	rs493871	Neta et al. 2011 (25)	$1.42 \times 10^{-4}$	—	0.36	0.74
<i>BCL2</i>	rs1801018; Thr7Thr	Eun et al. 2011 (34)	0.04	—	0.96	0.99
<i>BCL2</i>	rs2279115	Wang et al. 2012 (35)	0.01	0.07	0.77	0.92
<i>CDKN2A</i>	rs3731217	Zhang et al. 2013 (36)	$1.39 \times 10^{-3}$	—	0.82	0.92
<i>MDM2</i>	rs2279744	Zhang et al. 2013 (36)	0.01	—	0.28	0.70
<i>TGFB1</i>	rs1800472; Thr263Ile	Sigurdson et al. 2009 (27)	0.01	—	0.38	0.74
<i>TP53</i>	rs1042522; Pro72Arg	Granja et al. 2004 (37)	$3.12 \times 10^{-3}$	0.05	0.50	0.85
<i>WDR3</i>	rs4658973	Baida et al., 2008 (38)	$3.91 \times 10^{-8}$	$7.07 \times 10^{-6}$	0.04	0.24
Xenobiotic metabolism						
<i>CYP1A1</i>	rs4646903; 3801T>C	Bufalo et al. 2006 (39)	0.01	0.11	0.09	0.43
<i>CYP1A1</i>	rs1799814; 4887C>A	Siraj et al. 2008 (40)	$1.50 \times 10^{-5}$	—	$1.00 \times 10^{-3}$	<b>0.018</b>
<i>CYP19A1</i>	rs4774585	Schonfeldt et al. 2012 (41)	$2.64 \times 10^{-3}$	—	0.74	0.92
<i>CYP19A1</i>	rs1004984	Schonfeldt et al. 2012 (41)	0.01	—	0.19	0.68
<i>CYP19A1</i>	rs7163193	Schonfeldt et al. 2012 (41)	0.04	—	0.89	0.95
<i>CYP19A1</i>	rs2414099	Schonfeldt et al. 2012 (41)	0.01	—	0.12	0.51
<i>CYP8B1</i>	rs6788947	Asc.-Kilfoy et al. 2012 (42)	$6.58 \times 10^{-4}$	—	0.82	0.92
<i>CYP8B1</i>	rs7614670	Asc.-Kilfoy et al. 2012 (42)	0.02	—	0.71	0.92
<i>CYP8B1</i>	rs11715464	Asc.-Kilfoy et al. 2012 (42)	$4.71 \times 10^{-3}$	—	0.93	0.98
<i>FMO3</i>	rs10911641	Asc.-Kilfoy et al. 2012 (42)	0.03	—	0.46	0.83
<i>GSTP1</i>	rs1695	Granja et al. 2004 (43)	$3.21 \times 10^{-4}$	0.77	0.47	0.83
<i>MTF2</i>	rs549938	Asc.-Kilfoy et al. 2012 (42)	0.01	—	0.34	0.74
<i>MTHFR</i>	rs1801133	Prasad et al. 2011 (44)	0.04	0.03	0.24	0.70
<i>NAT2</i>	rs1799929; Leu161Leu	Hernández et al. 2008 (45)	0.01	—	0.73	0.92
<i>NAT2</i>	rs1041983; Tyr94Tyr	Guilhen et al. 2009 (46)	$1.76 \times 10^{-9}$	—	0.69	0.92
<i>NAT2</i>	rs1208; Arg268Lys	Guilhen et al. 2009 (46)	0.01	—	0.97	0.99
<i>SOD1</i>	rs1041740	Asc.-Kilfoy et al. 2012 (42)	$2.00 \times 10^{-3}$	—	0.23	0.70
<i>SOD1</i>	rs12626475	Asc.-Kilfoy et al. 2012 (42)	$3.39 \times 10^{-3}$	—	0.27	0.70
<i>UGT2B7</i>	rs3924194	Asc.-Kilfoy et al. 2012 (42)	0.01	—	0.28	0.70
Thyroid function						
<i>TG</i>	rs180223; Ser734Ala	Akdi et al. 2011 (47)	$4.26 \times 10^{-4}$	—	0.28	0.70
<i>TG</i>	rs853326; Met1028Val	Akdi et al. 2011 (47)	$3.92 \times 10^{-4}$	—	0.44	0.83
<i>THRA</i>	rs939348	Pastor et al. 2012 (48)	0.02	—	0.80	0.92
<i>TPO</i>	rs732609; Thr725Pro	Cipollini et al. 2013 (49)	$5.90 \times 10^{-3}$	0.12	0.65	0.92
<i>TPO</i>	rs2048722	Cipollini et al. 2013 (49)	0.03	0.26	0.84	0.93
MAPK pathway						
<i>HRAS</i>	rs12628; 81T>C	Khan et al. 2013 (50)	$7.66 \times 10^{-16}$	—	0.02	0.16
<i>PDGFRA</i>	rs6554162; -1309A>G	Kim et al. 2012 (51)	$6.62 \times 10^{-4}$	—	0.66	0.92
<i>PDGFRA</i>	rs1800812; -635G>T	Kim et al. 2012 (51)	0.01	—	0.63	0.92
<i>RET</i>	rs1800860; Ala432Ala	Ho et al. 2005 (52)	0.01	—	0.38	0.74
Immune response and inflammation						
<i>ALOX12</i>	rs1126667; Gln261Arg	Prasad et al. 2012 (53)	$7.79 \times 10^{-8}$	—	0.94	0.98
<i>IL1B</i>	rs1143627; -31C>T	Ban et al. 2012 (54)	0.04	—	0.62	0.92
<i>IL1B</i>	rs1143643	Ban et al. 2012 (54)	0.02	—	0.89	0.95
<i>IL1RA</i>	rs1061758; -106A>G	Eun et al. 2012 (55)	$2.21 \times 10^{-3}$	—	0.03	0.21
<i>MASPI</i>	rs850316	Brenner et al., 2013 (56)	$1.31 \times 10^{-3}$	—	0.28	0.70
<i>SERPINA5</i>	rs6112; Pro159Pro	Brenner et al., 2013 (56)	$4.27 \times 10^{-4}$	—	0.81	0.92
<i>SERPINA5</i>	rs6108	Brenner et al., 2013 (56)	$8.41 \times 10^{-5}$	—	0.69	0.92
<i>TICAM1</i>	rs2292151; Asp557Asp	Brenner et al., 2013 (56)	0.01	—	0.04	0.24
Other cancer genes						
<i>ATG16L1</i>	rs2241880; Thr300Ala	Huijbers et al. 2012 (57)	0.02	—	0.03	0.21
<i>BMP3</i>	rs3733549; Arg192Gln	Kim et al. 2013 (58)	0.02	—	0.47	0.83
<i>CDH1</i>	rs16260; -160C>A	Wang et al. 2012 (59)	$3.32 \times 10^{-3}$	—	0.35	0.74
<i>COL11A1</i>	rs1763347; Gly1516Gly	Park et al. 2011 (60)	$4.67 \times 10^{-3}$	—	0.59	0.92
<i>COL11A1</i>	rs2229783; Ile1602Ile	Park et al. 2011 (60)	0.01	—	0.70	0.92

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**Table 1.** List of SNPs associated with the risk of DTC in previous studies published in the literature (Cont'd)

Gene or Locus	dbSNP ID; variant	Author, year	Literature best $P_{\text{ass}}$	Meta-analysis of the literature	GWAS allelic $P_{\text{ass}}$	GWAS allelic $q$
<i>ESR1</i>	rs2228480; Thr594Thr	Rebâi et al. 2009 (61)	$1.51 \times 10^{-16}$	—	0.05	0.28
<i>FTO</i>	rs17817288	Kitahara et al. 2012 (62)	$9.75 \times 10^{-4}$	—	0.005	0.064
<i>FTO</i>	rs11642841	Kitahara et al. 2012 (62)	0.01	—	0.006	0.067
<i>FTO</i>	rs1121980	Kitahara et al. 2012 (62)	$4.86 \times 10^{-3}$	—	0.001	<b>0.018</b>
<i>FTO</i>	rs9939609	Kitahara et al. 2012 (62)	$4.36 \times 10^{-3}$	—	0.004	0.06
<i>FTO</i>	rs1477196	Kitahara et al. 2012 (62)	$3.44 \times 10^{-3}$	—	0.23	0.70
<i>GNB3</i>	rs5443; 825C>T	Sheu et al. 2007 (63)	0.03	—	0.51	0.85
<i>HDAC4</i>	rs6749348	Neta et al. 2011 (25)	$1.37 \times 10^{-4}$	—	0.29	0.71
<i>HDAC4</i>	rs7584828	Neta et al. 2011 (25)	$1.36 \times 10^{-3}$	—	0.10	0.45
<i>HER2</i>	rs1801200; Ile655Val	Rebâi et al. 2009 (64)	0.01	—	0.99	0.99
<i>IGF1R</i>	rs2229765; Glu1043Glu	Cho et al. 2012 (65)	$3.49 \times 10^{-3}$	—	0.51	0.85
<i>IGFBP3</i>	rs2132572	Xu et al. 2012 (66)	$3.87 \times 10^{-3}$	—	0.37	0.74
<i>IGFBP3</i>	rs2854744	Xu et al. 2012 (66)	0.04	—	0.99	0.99
<i>INSR</i>	rs919275	Kitahara et al. 2012 (62)	0.02	—	0.73	0.92
<i>ITGA6</i>	rs11895564; Ala380Thr	Kim et al. 2011 (67)	$5.00 \times 10^{-3}$	—	0.16	0.63
<i>ITGB2</i>	rs2070946; -149A>G	Eun et al. 2013 (68)	$1.27 \times 10^{-3}$	—	0.63	0.92
<i>MDR1</i>	rs1045642; Ile1145Ile	Ozdemir et al. 2013 (69)	$5.01 \times 10^{-4}$	—	0.09	0.43
<i>OPN</i>	rs11730582; -443C>T	Mu et al. 2013 (70)	0.03	—	0.69	0.92
<i>PTPRJ</i>	rs4752904; Asp872Glu	Iuliano et al. 2010 (71)	$5.00 \times 10^{-3}$	—	0.43	0.82
<i>SULF1</i>	rs6472462	Schonfeldt et al. 2012 (41)	0.01	—	0.35	0.74
<i>VEGFA</i>	rs699947; -2578C>A	Hsiao et al. 2007 (72)	0.01	—	0.06	0.32
<i>WVWX</i>	rs3764340; Pro282Ala	Cancemi et al. 2011 (73)	$5.40 \times 10^{-3}$	—	0.36	0.74
GWAS or intergenic regions						
1p12-13	rs2145418	Baida et al. 2008 (38)	$8.78 \times 10^{-10}$	—	0.77	0.92
1p31.3	rs334725	Gudmundsson et al. 2012 (15)	$6.60 \times 10^{-3}$	—	0.11	0.45
2q35	rs966423	Gudmundsson et al. 2012 (15)	$1.30 \times 10^{-9}$	$1.06 \times 10^{-6}$	0.009	0.09
5q24	rs2910164	Jazdzewski et al. 2008 (74)	$1.13 \times 10^{-5}$	0.10	0.60	0.92
8p12	rs2439302	Gudmundsson et al. 2012 (15)	$2.00 \times 10^{-9}$	—	0.19	0.68
8q24	rs6983267	Jones et al. 2012 (75)	$4.66 \times 10^{-3}$	0.07	0.82	0.92
9q22	rs965513	Gudmundsson et al. 2009 (16)	$1.70 \times 10^{-27}$	$<10^{-20}$	$2.67 \times 10^{-10}$	<b><math>2.40 \times 10^{-8}</math></b>
9q22	rs7048394	Landa et al. 2009 (76)	$2.40 \times 10^{-4}$	—	$2.41 \times 10^{-6}$	<b><math>7.23 \times 10^{-5}</math></b>
9q22	rs894673	Landa et al. 2009 (76)	$2.20 \times 10^{-4}$	—	$1.45 \times 10^{-8}$	<b><math>6.53 \times 10^{-7}</math></b>
14q13	rs944289	Gudmundsson et al. 2009 (16)	$2.00 \times 10^{-9}$	$<10^{-20}$	0.01	0.09

NOTE: Only SNPs associated in a statistically significant way at the 0.05 level or below are reported. The best  $P_{\text{ass}}$  represents the lowest published  $P$  value of association for any model tested (i.e., dominant, additive, recessive, and allelic). When more than one study was published on the same SNP, a meta-analysis of the literature data was performed and the best  $P_{\text{ass}}$  in any model is reported, as well. For each SNP the allelic  $P_{\text{ass}}$  from the present GWAS and its  $q$ -value after FDR correction is also reported.  $q < 0.05$  are highlighted in bold.

\*Complete references are shown in the Supplementary data.

95% CI, 1.02–1.48 in the allelic model), but a high heterogeneity was found between the study population previously analyzed and the present study ( $P_{\text{het}} < 0.0001$ ). Thus, no significant evidence of association was identified in the meta-analysis using the random-effect model (Table 2).

#### SNPs within immune response and inflammation genes

Fifteen genes and 33 SNPs involved in immunity or in inflammation pathways were analyzed to identify susceptibility variants for DTC and eight significantly associated SNPs were published (Table 1). The present GWAS replicated the possible role of rs1126667 (*ALOX12*, OR = 1.34, 95% CI, 1.02–1.75; heterozygotes) and rs2292151 (*TICAM1*, OR = 1.69, 95% CI, 0.99–2.91; homozygotes; Table 2), as well as for rs1061758 (*IL11RA*, OR = 1.29, 95% CI, 1.02–1.65; allelic model; Table 3). The involvement of these SNPs in increasing the risk of DTC was further suggested by the meta-analyses. In particular, an OR = 1.74 (95% CI, 1.28–2.37,  $q = 8.9 \times 10^{-4}$ ; allelic model) for rs1126667, and OR = 1.24 (95% CI, 1.06–1.45,  $q = 0.01$ ; allelic model) for rs2292151 was observed in the meta-analysis with Caucasians studies, and an OR = 1.39 (95% CI, 1.14–1.70,  $q = 0.01$ ; allelic model) for 1061758 was observed in the meta-analysis with an Asian study (Tables 2 and 3).

#### SNPs within other cancer genes

Fifty-five SNPs in 28 other genes related to cancer were investigated in relation to DTC risk and 37 SNPs were associated according to the literature. Of them, SNPs within *ATG16L1* and *FTO* showed a strong association in GWAS under the allelic model and rs1121980 (within *FTO*) remained associated also after FDR correction (Table 1). According to the present meta-analysis of the published results and our GWAS data on Caucasians, SNPs rs2241880 (*ATG16L1*, OR = 0.81, 95% CI, 0.70–0.93,  $q = 7.6 \times 10^{-3}$ ; allelic model), rs11642841 (*FTO*, OR = 0.76, 95% CI, 0.67–0.87,  $q = 1.2 \times 10^{-4}$ ; allelic model), rs1121980 (*FTO*, OR = 0.75, 95% CI, 0.66–0.86,  $q = 5.7 \times 10^{-5}$ ; allelic model), rs8050136 (*FTO*, OR = 0.76, 95% CI, 0.67–0.86,  $q = 4.8 \times 10^{-5}$ ; allelic model), rs9939609 (*FTO*, OR = 0.77, 95% CI, 0.67–0.88,  $q = 3.9 \times 10^{-4}$ ; allelic model), rs7202116 (*FTO*, OR = 0.76, 95% CI, 0.66–0.87,  $q = 2.5 \times 10^{-4}$ ; allelic model), rs7584828 (*HDAC4*, OR = 0.68, 95% CI, 0.54–0.84,  $q = 4.2 \times 10^{-3}$ ; heterozygotes), rs2132572 (5' region near *IGFBP3*, OR = 0.77, 95% CI, 0.61–0.96, only dominant model was available for meta-analysis), and rs17849071 (*PIK3CA*, OR = 0.64, 95% CI, 0.46–0.90,  $q = 0.04$ ; heterozygotes) were associated with a reduced risk of DTC, whereas SNPs rs17817288 (*FTO*, OR = 1.32, 95% CI, 1.15–1.51,  $q = 1.6 \times 10^{-4}$ ; allelic model) and rs6472462

**Table 2.** Meta-analyses of published data on Caucasians with data from present GWAS

Gene or locus	dbSNP ID	Reference	Published OR (allelic model)	Allelic OR (present GWAS)	Meta-analysis	$P_{\text{test}}$	$q$	Published OR (additive model)	OR of the additive model (present GWAS)	Meta-analysis	$P_{\text{test}}$	$q$
<b>DNA repair</b>												
<i>ATM</i>	rs664677	Akulevich et al. 2009 (77)	1.08 (0.87-1.33)	1.09 (0.90-1.32)	1.09 (0.94-1.25)	0.25	0.31	1.06 (0.76-1.47) <sup>a</sup>	1.07 (0.83-1.38) <sup>a</sup>	1.07 (0.87-1.30) <sup>a</sup>	0.53	0.57
	rs16942	Sturjgis et al. 2005 (32)	0.73 (0.51-1.05)	1.04 (0.86-1.25)	0.92 (0.81-1.06)	0.24	0.30	1.20 (0.75-1.91) <sup>b</sup>	1.23 (0.78-1.93) <sup>b</sup>	1.22 (0.88-1.69) <sup>b</sup>	0.24	0.40
<i>BRCA1</i>		Xu et al. 2012 (26)	0.85 (0.68-1.06)					0.80 (0.49-1.29) <sup>a</sup>	1.40 (0.80-1.34) <sup>a</sup>	0.88 (0.74-1.06) <sup>a</sup>	0.18	0.29
								0.41 (0.15-1.10) <sup>b</sup>	1.08 (0.72-1.61) <sup>b</sup>	0.91 (0.68-1.23) <sup>b</sup>	0.56	0.63
<b>HUS1</b>												
<i>HUS1</i>	rs2708906	Neira et al. 2011 (25)	—	1.11 (0.93-1.32)	—	—	—	<b>1.55 (1.11-2.18)<sup>a</sup></b>	1.21 (0.91-1.61) <sup>a</sup>	<b>1.34 (1.08-1.67)<sup>a</sup></b>	$8.8 \times 10^{-3}$	0.04
	rs25487	Siraj et al. 2008 (28)	0.72 (0.41-1.26)	0.87 (0.72-1.05)	<b>0.92 (0.85-0.99)</b>	0.04	0.06	<b>2.40 (1.51-3.82)<sup>b</sup></b>	1.70 (0.92-1.57) <sup>b</sup>	<b>1.52 (1.16-2.00)<sup>b</sup></b>	$2.5 \times 10^{-3}$	0.01
		Ho et al. 2009 (31)	<b>0.70 (0.56-0.89)</b>					—	0.87 (0.58-1.34) <sup>b</sup>	0.85 (0.71-1.02) <sup>b</sup>	0.11	0.22
		Sigurdson et al. 2009 (27)	1.05 (0.91-1.21)					0.76 (0.55-1.05) <sup>a</sup>			0.07	0.17
		Akulevich et al. 2009 (77)	0.86 (0.69-1.07)					<b>0.47 (0.27-0.82)<sup>b</sup></b>				
		García-Qu. et al. 2011 (30)	1.00 (0.82-1.22)					0.95 (0.68-1.32) <sup>b</sup>				
		Fard-Esf. et al. 2011 (78)	0.87 (0.63-1.20)					<b>0.68 (0.50-0.94)<sup>a</sup></b>				
		Santos et al. 2012 (79)	0.96 (0.69-1.35)					0.90 (0.56-1.45) <sup>b</sup>				
								1.12 (0.84-1.50) <sup>a</sup>				
								0.91 (0.59-1.40) <sup>b</sup>				
								0.73 (0.47-1.15) <sup>a</sup>				
								0.90 (0.44-1.85) <sup>b</sup>				
								0.90 (0.55-1.47) <sup>a</sup>				
								0.98 (0.46-2.10) <sup>b</sup>				
<i>XRCC3</i>	rs1799796	García-Qu. et al. 2011 (30)	0.85 (0.68-1.06)	0.86 (0.70-1.06)	<b>0.86 (0.73-1.00)</b>	0.04	0.06	0.92 (0.69-1.21) <sup>a</sup>	0.80 (0.62-1.03) <sup>a</sup>	0.85 (0.71-1.03) <sup>a</sup>	0.46	0.52
	rs7830743	Siraj et al. 2008 (28)	0.99 (0.65-1.49)	1.07 (0.78-1.47)	<b>1.24 (1.01-1.54)</b>	0.04	0.06	0.60 (0.33-1.11) <sup>b</sup>	0.87 (0.51-1.48) <sup>b</sup>	0.74 (0.50-1.11) <sup>b</sup>	0.37	0.44
		Rahimi et al. 2012 (33)	1.90 (1.29-2.79)					1.11 (0.27-4.49) <sup>b</sup>	1.12 (0.27-4.72) <sup>b</sup>	1.13 (0.49-2.61) <sup>b</sup>	0.78	0.81
								<b>2.42 (1.55-3.81)<sup>a</sup></b>				
								1.16 (0.25-5.29) <sup>b</sup>				
<i>ZNF550</i>	rs2278420	Sigurdson et al. 2009 (27)	0.99 (0.84-1.16)	0.85 (0.67-1.09)	0.95 (0.83-1.08)	0.27	0.31	1.05 (0.86-1.28) <sup>a</sup>	0.86 (0.65-1.13) <sup>a</sup>	0.98 (0.84-1.15) <sup>a</sup>	0.81	0.83
								0.83 (0.53-1.32) <sup>b</sup>	0.70 (0.29-1.66) <sup>b</sup>	0.80 (0.53-1.20) <sup>b</sup>	0.28	0.41
<b>Cell-cycle regulation and apoptosis</b>												
<i>WDR3</i>	rs4658973	Baida et al. 2008 (38)	<b>0.35 (0.25-0.47)</b>	<b>0.83 (0.70-1.00)</b>	<b>0.71 (0.61-0.82)</b>	$5.7 \times 10^{-6}$	$1.8 \times 10^{-6}$	<b>0.40 (0.26-0.62)<sup>a</sup></b>	<b>0.65 (0.49-0.86)<sup>a</sup></b>	<b>0.60 (0.48-0.74)<sup>a</sup></b>	$3.7 \times 10^{-6}$	$7.8 \times 10^{-5}$
		Akdi et al. 2010 (80)	1.09 (0.77-1.55)					<b>0.07 (0.03-0.18)<sup>b</sup></b>	0.74 (0.52-1.06) <sup>b</sup>	<b>0.64 (0.47-0.87)<sup>b</sup></b>	$4.5 \times 10^{-3}$	$1.7 \times 10^{-2}$
								0.81 (0.46-1.41) <sup>b</sup>				
								1.29 (0.63-2.64) <sup>b</sup>				
<b>Xenobiotic metabolism</b>												
<i>CYP1A1</i>	rs4646903	Siraj et al. 2008 (40)	1.42 (0.88-2.30)	1.28 (0.95-1.73)	—	—	—	1.16 (0.60-2.24) <sup>a</sup>	1.32 (0.96-1.80) <sup>a</sup>	1.29 (0.97-1.71) <sup>a</sup>	0.12	0.23
	rs1799814	Siraj et al. 2008 (40)	<b>1.87 (1.44-2.42)</b>	<b>1.85 (1.27-2.70)</b>	<b>1.86 (1.50-2.30)</b>	$1.3 \times 10^{-8}$	$4.4 \times 10^{-8}$	<b>1.91 (1.36-2.70)<sup>b</sup></b>	<b>1.77 (1.20-2.60)<sup>b</sup></b>	<b>1.85 (1.43-2.39)<sup>b</sup></b>	0.29	0.41
	rs12622950	Asc.-Kilfoy et al. 2012 (42)	—	1.10 (0.88-1.38)	—	—	—	<b>3.48 (1.74-6.96)<sup>b</sup></b>	<b>5.03 (0.62-41.1)<sup>b</sup></b>	<b>3.61 (1.87-6.97)<sup>b</sup></b>	$1.3 \times 10^{-4}$	$1.1 \times 10^{-3}$
	rs1606254	Asc.-Kilfoy et al. 2012 (42)	—	1.14 (0.89-1.46)	—	—	—	1.32 (0.96-1.83) <sup>b</sup>	1.04 (0.79-1.36) <sup>b</sup>	1.14 (0.93-1.41) <sup>b</sup>	0.20	0.29
	rs707718	Asc.-Kilfoy et al. 2012 (42)	—	0.99 (0.79-1.25)	—	—	—	1.69 (0.72-3.95) <sup>b</sup>	1.41 (0.76-2.60) <sup>b</sup>	1.50 (0.91-2.46) <sup>b</sup>	0.11	0.24
								2.07 (0.80-5.34) <sup>b</sup>	1.57 (0.64-3.87) <sup>b</sup>	1.79 (0.93-3.44) <sup>b</sup>	0.68	0.73
								0.80 (0.57-1.13) <sup>a</sup>	0.90 (0.69-1.17) <sup>a</sup>	0.86 (0.70-1.06) <sup>a</sup>	0.16	0.28
								2.05 (0.86-4.91) <sup>b</sup>	1.51 (0.68-3.35) <sup>b</sup>	1.74 (0.96-3.31) <sup>b</sup>	0.07	0.17
<i>MTHFR</i>	rs1801133	Siraj et al. 2008 (40)	1.47 (0.87-2.47)	1.11 (0.93-1.33)	<b>1.18 (1.00-1.69)</b>	0.05	0.08	1.77 (0.96-3.29) <sup>a</sup>	1.20 (0.90-1.60) <sup>a</sup>	<b>1.34 (1.05-1.73)<sup>a</sup></b>	0.02	0.07
		Prasad et al. 2011 (44)	<b>2.20 (1.00-4.86)</b>					0.95 (0.12-7.54) <sup>b</sup>	1.21 (0.86-1.71) <sup>b</sup>	<b>1.22 (0.87-1.71)<sup>b</sup></b>	0.26	0.40
								2.21 (0.92-5.30) <sup>a</sup>				
								2.65 (0.16-42.9) <sup>b</sup>				
<i>MAT2</i>	rs1799929	Hernández et al. 2008 (45)	<b>0.70 (0.51-0.96)</b>	0.97 (0.81-1.16)	0.89 (0.76-1.05)	0.16	0.23	<b>0.51 (0.27-0.96)<sup>b</sup></b>	0.85 (0.64-1.11) <sup>a</sup>	0.80 (0.63-1.02) <sup>a</sup>	0.07	0.17
	rs104740	Asc.-Kilfoy et al. 2012 (42)	<b>1.42 (1.14-1.76)</b>	1.12 (0.93-1.34)	<b>1.23 (1.08-1.42)</b>	$2.7 \times 10^{-3}$	$5.5 \times 10^{-3}$	<b>1.48 (1.09-2.00)<sup>a</sup></b>	1.20 (0.92-1.57) <sup>b</sup>	<b>1.32 (1.08-1.61)<sup>a</sup></b>	$7.1 \times 10^{-3}$	0.04
	rs12626475	Asc.-Kilfoy et al. 2012 (42)	<b>1.33 (1.08-1.64)</b>	1.10 (0.92-1.33)	<b>1.20 (1.04-1.38)</b>	0.01	0.02	<b>1.86 (1.15-3.02)<sup>b</sup></b>	1.17 (0.80-1.71) <sup>b</sup>	<b>1.40 (1.04-1.88)<sup>b</sup></b>	0.03	0.09
								1.33 (0.98-1.79) <sup>a</sup>	1.18 (0.91-1.54) <sup>a</sup>	<b>1.24 (1.02-1.52)<sup>a</sup></b>	0.03	0.09
								<b>1.73 (1.09-2.73)<sup>b</sup></b>	1.16 (0.80-1.69) <sup>b</sup>	<b>1.36 (1.02-1.82)<sup>b</sup></b>	0.04	0.11

(Continued on the following page)

Table 2. Meta-analyses of published data on Caucasians with data from present GWAS (Cont'd)

Gene or locus	dbSNP ID	Reference	Published OR (allelic model)	Allelic OR (present GWAS)	Meta-analysis	$P_{\text{GWAS}}$	$q$	Published OR (additive model)	OR of the additive model (present GWAS)	Meta-analysis	$P_{\text{GWAS}}$	$q$
<i>UGT2B7</i>	rs5924194	Asc.-Kilfoy et al. 2012 (42)	<b>0.66 (0.49-0.88)</b>	0.84 (0.61-1.16)	—	—	—	<b>0.31 (0.12-0.85)<sup>b</sup></b>	0.97 (0.16-5.82) <sup>b</sup>	<b>0.37 (0.15-0.91)<sup>b</sup></b>	0.03	0.09
<b>Thyroid function</b>												
<i>THRβ</i>	rs828377	Pastor et al. 2012 (48)	1.01 (0.79-1.29)	1.00 (0.81-1.24)	1.06 (0.94-1.21)	0.35	0.38	1.08 (0.81-1.45) <sup>a</sup>	1.13 (0.87-1.46) <sup>b</sup>	1.11 (0.91-1.34) <sup>b</sup>	0.30	0.39
<i>TPO</i>	rs1042589	Cipollini et al. 2013 (49)	0.94 (0.84-1.05)	0.89 (0.74-1.06)	0.93 (0.85-1.02)	0.12	0.17	0.98 (0.81-1.18) <sup>a</sup>	0.76 (0.56-1.03) <sup>a</sup>	0.92 (0.79-1.06) <sup>a</sup>	0.24	0.33
		Cipollini et al. 2013 (49)	0.94 (0.78-1.14)	—	—	—	—	0.87 (0.69-1.10) <sup>b</sup>	0.78 (0.54-1.11) <sup>b</sup>	0.86 (0.73-1.03) <sup>b</sup>	0.10	0.23
								0.88 (0.65-1.19) <sup>a</sup>	0.90 (0.62-1.32) <sup>b</sup>	—	—	—
<i>TRHR</i>	rs4129682	Akdi et al. 2011 (47)	0.99 (0.82-1.19)	0.88 (0.74-1.05)	0.93 (0.82-1.37)	0.27	0.31	1.15 (0.83-1.58) <sup>a</sup>	1.09 (0.83-1.44) <sup>a</sup>	1.12 (0.90-1.38) <sup>a</sup>	0.31	0.39
<i>TRHR</i>	rs7823804	Akdi et al. 2011 (47)	0.94 (0.77-1.14)	0.94 (0.77-1.14)	0.94 (0.82-1.08)	0.37	0.39	0.96 (0.65-1.41) <sup>b</sup>	0.74 (0.52-1.04) <sup>b</sup>	0.83 (0.64-1.07) <sup>b</sup>	0.15	0.32
<i>TSHR</i>	rs1845164	Pastor et al. 2012 (48)	1.08 (0.83-1.41)	1.21 (0.91-1.61)	1.14 (0.94-1.38)	0.19	0.26	0.91 (0.69-1.22) <sup>a</sup>	1.03 (0.80-1.34) <sup>a</sup>	0.97 (0.80-1.19) <sup>a</sup>	0.80	0.83
<i>TSHR</i>	rs8019570	Pastor et al. 2012 (48)	1.09 (0.83-1.42)	1.21 (0.91-1.61)	1.14 (0.94-1.39)	0.17	0.23	0.89 (0.57-1.41) <sup>b</sup>	<b>1.37 (1.00-1.88)<sup>a</sup></b>	0.84 (0.62-1.15) <sup>b</sup>	0.27	0.41
<i>HRAS</i>	rs12628	Khan et al. 2013 (50)	<b>5.82 (3.80-8.93)</b>	<b>1.23 (1.02-1.48)</b>	2.64 (0.58-12.1)	0.21	0.27	2.22 (0.81-6.07) <sup>b</sup>	0.70 (0.26-1.89) <sup>b</sup>	1.24 (0.61-2.51) <sup>b</sup>	0.55	0.62
<i>RET</i>	rs1799939	He et al. 2005 (52)	0.79 (0.50-1.25)	1.14 (0.92-1.41)	1.05 (0.93-1.19)	0.43	0.44	0.99 (0.73-1.35) <sup>a</sup>	<b>1.37 (1.00-1.88)<sup>a</sup></b>	1.16 (0.93-1.45) <sup>a</sup>	0.19	0.29
		Sigurdson et al. 2009 (27)	1.04 (0.88-1.23)	—	—	—	—	2.04 (0.73-5.7) <sup>b</sup>	0.70 (0.26-1.89) <sup>b</sup>	1.18 (0.58-2.40) <sup>b</sup>	0.65	0.72
								<b>6.66 (3.66-12.1)<sup>a</sup></b>	<b>1.51 (1.16-1.96)<sup>a</sup></b>	3.09 (0.72-13.2) <sup>a</sup>	0.13	0.24
								<b>9.86 (4.08-23.8)<sup>b</sup></b>	1.31 (0.89-1.92) <sup>b</sup>	3.45 (0.48-24.9) <sup>b</sup>	0.22	0.40
								0.67 (0.38-1.19) <sup>b</sup>	1.29 (0.99-1.67) <sup>a</sup>	1.08 (0.92-1.25) <sup>a</sup>	0.35	0.43
								0.97 (0.32-3.07) <sup>b</sup>	0.93 (0.51-1.67) <sup>b</sup>	1.04 (0.72-1.50) <sup>b</sup>	0.84	0.86
								1.02 (0.84-1.25) <sup>a</sup>	—	—	—	—
								1.15 (0.69-1.93) <sup>b</sup>	—	—	—	—
<b>Immune response and inflammation</b>												
<i>ALOX12</i>	rs126667	Prasad et al. 2012 (53)	<b>2.06 (1.45-2.93)</b>	0.99 (0.83-1.89)	<b>1.74 (1.28-2.37)</b>	4.0 × 10 <sup>-4</sup>	8.9 × 10 <sup>-4</sup>	<b>3.01 (1.88-4.82)<sup>a</sup></b>	<b>1.34 (1.02-1.75)<sup>a</sup></b>	<b>1.63 (1.29-2.06)<sup>a</sup></b>	4.3 × 10 <sup>-5</sup>	6.0 × 10 <sup>-4</sup>
<i>SERPINA5</i>	rs6115	Brenner et al. 2013 (56)	<b>1.72 (1.40-2.12)</b>	1.02 (0.85-1.24)	1.32 (0.79-2.21)	0.28	0.31	2.75 (0.49-15.6) <sup>b</sup>	0.85 (0.59-1.22) <sup>b</sup>	0.89 (0.63-1.27) <sup>b</sup>	0.53	0.62
<i>SERPINA5</i>	rs6112	Brenner et al. 2013 (56)	<b>1.61 (1.31-1.99)</b>	1.02 (0.85-1.24)	1.28 (0.82-2.00)	0.28	0.31	<b>1.76 (1.29-2.41)<sup>b</sup></b>	1.09 (0.84-1.41) <sup>b</sup>	1.37 (0.86-2.19) <sup>b</sup>	0.19	0.29
<i>SERPINA5</i>	rs6108	Brenner et al. 2013 (56)	<b>1.48 (1.20-1.81)</b>	1.04 (0.86-1.26)	1.24 (0.88-1.75)	0.22	0.28	<b>2.52 (1.66-3.87)<sup>b</sup></b>	0.98 (0.65-1.49) <sup>b</sup>	1.57 (0.62-3.97) <sup>b</sup>	0.34	0.43
<i>TICAM1</i>	rs2292151	Brenner et al. 2013 (56)	<b>1.46 (1.16-1.84)</b>	1.09 (0.89-1.34)	<b>1.24 (1.06-1.45)</b>	7.1 × 10 <sup>-3</sup>	0.01	<b>1.76 (1.30-2.37)<sup>b</sup></b>	1.09 (0.84-1.41) <sup>b</sup>	1.38 (0.86-2.20) <sup>b</sup>	0.18	0.29
								<b>2.74 (1.63-4.62)<sup>b</sup></b>	0.98 (0.65-1.49) <sup>b</sup>	1.62 (0.59-4.43) <sup>b</sup>	0.35	0.43
								<b>1.99 (1.02-1.89)<sup>b</sup></b>	1.09 (0.84-1.41) <sup>b</sup>	1.21 (0.96-1.54) <sup>b</sup>	0.11	0.22
								<b>1.43 (1.06-1.93)<sup>b</sup></b>	1.02 (0.67-1.56) <sup>b</sup>	1.56 (0.67-3.63) <sup>b</sup>	0.30	0.41
								<b>2.15 (1.19-3.88)<sup>b</sup></b>	1.69 (0.99-2.91) <sup>b</sup>	<b>1.89 (1.27-2.82)<sup>b</sup></b>	1.8 × 10 <sup>-3</sup>	0.01
<b>Other cancer genes</b>												
<i>ATG16L1</i>	rs224880	Huijbers et al. 2012 (57)	<b>0.76 (0.60-0.98)</b>	<b>0.83 (0.70-0.99)</b>	<b>0.81 (0.70-0.93)</b>	3.6 × 10 <sup>-3</sup>	7.6 × 10 <sup>-3</sup>	0.67 (0.44-1.01) <sup>b</sup>	0.97 (0.73-1.30) <sup>a</sup>	0.86 (0.68-1.08) <sup>a</sup>	0.19	0.29
<i>FTO</i>	rs1781288	Kitahara et al. 2012 (62)	<b>1.37 (1.12-1.68)</b>	1.28 (1.07-1.53)	<b>1.32 (1.15-1.51)</b>	6.4 × 10 <sup>-5</sup>	1.6 × 10 <sup>-4</sup>	<b>0.57 (0.35-0.83)<sup>b</sup></b>	<b>0.67 (0.47-0.95)<sup>b</sup></b>	<b>0.63 (0.48-0.84)<sup>b</sup></b>	1.7 × 10 <sup>-3</sup>	0.01
<i>FTO</i>	rs11642841	Kitahara et al. 2012 (62)	<b>0.74 (0.60-0.91)</b>	<b>0.78 (0.65-0.93)</b>	<b>0.76 (0.67-0.87)</b>	3.8 × 10 <sup>-5</sup>	1.2 × 10 <sup>-4</sup>	<b>1.98 (1.30-3.02)<sup>b</sup></b>	1.31 (0.99-1.74) <sup>b</sup>	<b>1.36 (1.09-1.71)<sup>b</sup></b>	6.8 × 10 <sup>-3</sup>	0.04
<i>FTO</i>	rs1121980	Kitahara et al. 2012 (62)	<b>0.76 (0.62-0.93)</b>	<b>0.75 (0.63-0.89)</b>	<b>0.75 (0.66-0.86)</b>	2.0 × 10 <sup>-5</sup>	5.7 × 10 <sup>-5</sup>	<b>0.64 (0.47-0.87)<sup>a</sup></b>	<b>0.88 (0.67-1.16)<sup>a</sup></b>	<b>0.76 (0.62-0.94)<sup>a</sup></b>	9.7 × 10 <sup>-3</sup>	0.04
<i>FTO</i>	rs8030136	Kitahara et al. 2012 (62)	<b>0.77 (0.62-0.94)</b>	<b>0.75 (0.65-0.89)</b>	<b>0.76 (0.67-0.86)</b>	1.6 × 10 <sup>-5</sup>	4.8 × 10 <sup>-5</sup>	<b>0.61 (0.40-0.94)<sup>b</sup></b>	<b>0.59 (0.42-0.84)<sup>b</sup></b>	<b>0.60 (0.45-0.79)<sup>b</sup></b>	3.7 × 10 <sup>-4</sup>	2.2 × 10 <sup>-3</sup>
<i>FTO</i>	rs9939609	Kitahara et al. 2012 (62)	<b>0.77 (0.62-0.94)</b>	<b>0.77 (0.65-0.93)</b>	<b>0.77 (0.67-0.88)</b>	1.7 × 10 <sup>-4</sup>	3.9 × 10 <sup>-4</sup>	<b>0.70 (0.51-0.96)<sup>a</sup></b>	0.84 (0.63-1.19) <sup>a</sup>	<b>0.76 (0.60-0.96)<sup>a</sup></b>	0.02	0.07
<i>FTO</i>	rs2202116	Kitahara et al. 2012 (62)	<b>0.77 (0.63-0.95)</b>	<b>0.75 (0.63-0.89)</b>	<b>0.76 (0.66-0.87)</b>	9.8 × 10 <sup>-5</sup>	2.5 × 10 <sup>-4</sup>	<b>0.60 (0.39-0.92)<sup>b</sup></b>	<b>0.55 (0.39-0.78)<sup>b</sup></b>	<b>0.57 (0.43-0.75)<sup>b</sup></b>	7.5 × 10 <sup>-5</sup>	7.9 × 10 <sup>-4</sup>
<i>HDAC4</i>	rs6749348	Neta et al. 2011 (25)	—	0.85 (0.62-1.16)	—	—	—	<b>0.59 (0.38-0.93)<sup>b</sup></b>	<b>0.55 (0.39-0.78)<sup>b</sup></b>	<b>0.56 (0.43-0.74)<sup>b</sup></b>	2.8 × 10 <sup>-5</sup>	6.7 × 10 <sup>-4</sup>
<i>HDAC4</i>	rs7584828	Neta et al. 2011 (25)	—	<b>0.82 (0.64-1.05)</b>	—	—	—	<b>0.74 (0.54-1.00)<sup>b</sup></b>	<b>0.88 (0.67-1.16)<sup>b</sup></b>	<b>0.81 (0.66-1.00)<sup>b</sup></b>	0.05	0.13
<i>IGFBP3</i>	rs2132572	Xu et al. 2012 (66) <sup>†</sup>	<b>0.60 (0.40-0.80)</b>	0.86 (0.66-1.13)	<b>0.77 (0.61-0.96)</b>	0.02	0.02	<b>0.60 (0.38-0.93)<sup>b</sup></b>	<b>0.58 (0.41-0.83)<sup>b</sup></b>	<b>0.59 (0.45-0.78)<sup>b</sup></b>	2.8 × 10 <sup>-4</sup>	1.9 × 10 <sup>-3</sup>
<i>PIK3CA</i>	rs17849071	Xing et al. 2012 (81)	—	0.71 (0.51-0.99)	—	—	—	<b>0.40 (0.28-0.65)<sup>b</sup></b>	0.78 (0.56-1.08) <sup>b</sup>	0.58 (0.31-1.08) <sup>b</sup>	0.09	0.20
<i>SULF1</i>	rs6472462	Schonfeld et al. 2012 (41)	<b>1.28 (1.05-1.56)</b>	1.09 (0.91-1.30)	<b>1.17 (1.03-1.33)</b>	0.02	0.03	<b>0.55 (0.38-0.79)<sup>a</sup></b>	1.92 (0.39-9.56) <sup>b</sup>	<b>0.67 (0.54-0.84)<sup>a</sup></b>	4.0 × 10 <sup>-4</sup>	4.2 × 10 <sup>-3</sup>
								0.33 (0.08-1.28) <sup>b</sup>	<b>0.96 (0.41-2.25)<sup>b</sup></b>	0.71 (0.35-1.46) <sup>b</sup>	0.35	0.43
								0.52 (0.23-1.19) <sup>b</sup>	0.67 (0.47-0.96) <sup>b</sup>	<b>0.64 (0.46-0.90)<sup>b</sup></b>	8.8 × 10 <sup>-3</sup>	0.04
								1.40 (0.97-2.02) <sup>a</sup>	0.92 (0.69-1.23) <sup>a</sup>	1.08 (0.86-1.36) <sup>a</sup>	0.50	0.55
								<b>1.67 (1.11-2.50)<sup>b</sup></b>	1.19 (0.84-1.68) <sup>b</sup>	<b>1.37 (1.06-1.78)<sup>b</sup></b>	0.02	0.07

(Continued on the following page)

**Table 2.** Meta-analyses of published data on Caucasians with data from present GWAS (Cont'd)

Gene or Locus GWAS or Intergenic regions	dbSNP ID	Reference	Published OR (allelic model)	Allelic OR (present GWAS)	Meta-analysis	$P_{\text{BS}}$	$q$	Published OR (additive model)	OR of the additive model (present GWAS)	Meta-analysis	$P_{\text{BS}}$	$q$
1p12-13	rs4659200	Baida et al. 2008 (38)	0.84 (0.61-1.15)	0.97 (0.81-1.17)	0.93 (0.80-1.10)	0.41	0.43	0.99 (0.62-1.60) <sup>a</sup>	1.15 (0.88-1.50) <sup>a</sup>	1.11 (0.88-1.40) <sup>a</sup>	0.38	0.46
		Baida et al. 2008 (38)	1.02 (0.78-1.34)	0.94 (0.79-1.12)	0.96 (0.83-1.12)	0.61	0.61	0.66 (0.35-1.26) <sup>b</sup>	0.85 (0.58-1.24) <sup>b</sup>	0.80 (0.58-1.10) <sup>b</sup>	0.17	0.34
		Baida et al. 2008 (38)	0.90 (0.65-1.25)	0.92 (0.76-1.10)	0.92 (0.78-1.07)	0.27	0.31	1.11 (0.62-1.97) <sup>b</sup>	0.89 (0.63-1.26) <sup>b</sup>	0.94 (0.70-1.27) <sup>b</sup>	0.09	0.20
1p12-13	rs1241	Gudmundsson et al. 2012 (15)	<b>1.31 (1.08-1.60)</b>	1.39 (0.91-2.13)	<b>1.32 (1.10-1.59)</b>	$2.4 \times 10^{-3}$	$5.1 \times 10^{-3}$	1.09 (0.44-1.10) <sup>a</sup>	1.09 (0.84-1.42) <sup>a</sup>	0.98 (0.77-1.23) <sup>a</sup>	0.83	0.83
		Gudmundsson et al. 2012 (15)	<b>1.34 (1.22-1.47)</b>	<b>1.26 (1.06-1.51)</b>	<b>1.27 (1.19-1.35)</b>	$1.0 \times 10^{-13}$	$1.3 \times 10^{-12}$	0.74 (0.48-1.16) <sup>b</sup>	0.73 (0.49-1.08) <sup>b</sup>	0.79 (0.55-1.13) <sup>b</sup>	0.20	0.38
2q35	rs966423	Gudmundsson et al. 2012 (15)	<b>1.30 (1.12-1.51)</b>	<b>1.26 (1.06-1.51)</b>	<b>1.27 (1.19-1.35)</b>	$1.0 \times 10^{-13}$	$1.3 \times 10^{-12}$	—	1.33 (0.86-2.05) <sup>a</sup>	—	—	—
		Liyanaarachchi et al. 2013 (82)	<b>1.30 (1.12-1.51)</b>	—	—	—	—	—	2.74 (0.30-24.6) <sup>b</sup>	—	—	—
5q24	rs2910164	Liyanaarachchi et al. 2013 (82)	<b>1.14 (1.01-1.29)</b>	—	—	—	—	—	<b>1.74 (1.21-2.50)<sup>b</sup></b>	—	—	—
		Jazdzewski et al. 2008 (74)	1.14 (0.96-1.34)	0.95 (0.78-1.16)	1.01 (0.93-1.09)	0.89	0.92	—	0.94 (0.73-1.22) <sup>a</sup>	1.07 (0.97-1.19) <sup>a</sup>	0.19	0.29
8p12	rs2439302	Jones et al. 2012 (75)	1.00 (0.88-1.14)	—	—	—	—	<b>1.55 (1.25-1.91)<sup>a</sup></b>	0.91 (0.56-1.47) <sup>b</sup>	0.88 (0.73-1.07) <sup>b</sup>	0.19	0.36
		Wei et al. 2013 (83)	0.95 (0.82-1.09)	—	—	—	—	1.01 (0.86-1.19) <sup>a</sup>	—	—	—	—
		Gudmundsson et al. 2012 (15)	<b>1.36 (1.23-1.50)</b>	1.12 (0.94-1.34)	<b>1.30 (1.23-1.39)</b>	$4.0 \times 10^{-17}$	$1.2 \times 10^{-15}$	0.98 (0.71-1.10) <sup>a</sup>	1.10 (0.83-1.45) <sup>a</sup>	—	—	—
8q24	rs6983267	Liyanaarachchi et al. 2013 (82)	<b>1.46 (1.26-1.70)</b>	—	—	—	—	—	1.28 (0.90-1.83) <sup>b</sup>	—	—	—
		Liyanaarachchi et al. 2013 (82)	<b>1.23 (1.09-1.38)</b>	1.02 (0.86-1.22)	1.06 (0.99-1.14)	0.09	0.13	—	1.14 (0.83-1.57) <sup>a</sup>	1.03 (0.73-1.46) <sup>b</sup>	0.65	0.70
9q22	rs965513	Akdi et al. 2011 (47)	0.98 (0.81-1.18)	—	—	—	—	0.94 (0.65-1.36) <sup>b</sup>	1.15 (0.56-1.54) <sup>a</sup>	1.11 (0.96-1.27) <sup>b</sup>	0.15	0.32
		Jones et al. 2012 (75)	<b>1.14 (1.03-1.27)</b>	—	—	—	—	1.01 (0.83-1.23) <sup>a</sup>	—	—	—	—
9q22	rs965513	Wang et al. 2013 (84)	1.01 (0.88-1.15)	—	—	—	—	<b>1.27 (1.03-1.57)<sup>b</sup></b>	0.99 (0.80-1.21) <sup>a</sup>	—	—	—
		Gudmundsson et al. 2009 (16)	<b>1.75 (1.59-1.94)</b>	<b>1.78 (1.48-2.14)</b>	<b>1.85 (1.76-1.95)</b>	$<10^{-20}$	$<10^{-20}$	1.01 (0.78-1.32) <sup>b</sup>	<b>1.80 (1.37-2.35)<sup>a</sup></b>	—	—	—
9q22	rs7048394	Takahashi et al. 2010 (17)	<b>1.65 (1.43-1.91)</b>	—	—	—	—	—	<b>3.08 (2.10-4.53)<sup>b</sup></b>	—	—	—
		Jones et al. 2012 (75)	<b>1.96 (1.76-2.18)</b>	—	—	—	—	—	—	—	—	—
9q22	rs3758249	Tomaz et al. 2012 (85)	<b>2.81 (1.87-4.22)</b>	—	—	—	—	—	—	—	—	—
		Liyanaarachchi et al. 2013 (82)	<b>2.09 (1.80-2.42)</b>	—	—	—	—	—	—	—	—	—
9q22	rs907577	Liyanaarachchi et al. 2013 (82)	<b>1.81 (1.59-2.06)</b>	—	—	—	—	—	—	—	—	—
		Landa et al. 2009 (76)	<b>1.46 (1.19-1.78)</b>	<b>1.55 (1.29-1.87)</b>	<b>1.51 (1.31-1.73)</b>	$6.3 \times 10^{-9}$	$2.3 \times 10^{-8}$	—	<b>1.39 (1.07-1.80)<sup>a</sup></b>	—	—	—
9q22	rs694673	Landa et al. 2009 (76)	<b>1.39 (1.17-1.65)</b>	<b>1.65 (1.38-1.97)</b>	<b>1.51 (1.33-1.71)</b>	$1.3 \times 10^{-10}$	$8.3 \times 10^{-10}$	—	<b>2.78 (1.80-4.28)<sup>b</sup></b>	—	—	—
		Landa et al. 2009 (76)	<b>1.39 (1.17-1.66)</b>	<b>1.65 (1.38-1.97)</b>	<b>1.51 (1.34-1.72)</b>	$1.3 \times 10^{-10}$	$8.3 \times 10^{-10}$	—	<b>2.92 (2.02-4.22)<sup>b</sup></b>	—	—	—
9q22	rs5021526	Landa et al. 2009 (76)	<b>1.32 (1.11-1.58)</b>	<b>1.65 (1.38-1.97)</b>	<b>1.51 (1.34-1.71)</b>	$1.3 \times 10^{-10}$	$8.3 \times 10^{-10}$	—	<b>2.92 (2.02-4.22)<sup>b</sup></b>	—	—	—
		Landa et al. 2009 (76)	<b>1.32 (1.11-1.58)</b>	<b>1.65 (1.38-1.97)</b>	<b>1.51 (1.34-1.71)</b>	$1.3 \times 10^{-10}$	$8.3 \times 10^{-10}$	—	<b>2.92 (2.02-4.22)<sup>b</sup></b>	—	—	—
9q22	rs1019760	Tomaz et al. 2012 (85)	<b>1.89 (1.27-2.82)</b>	—	—	—	—	—	—	—	—	—
		Landa et al. 2009 (76)	<b>1.47 (1.23-1.75)</b>	<b>1.65 (1.38-1.97)</b>	<b>1.56 (1.34-1.76)</b>	$1.6 \times 10^{-10}$	$9.7 \times 10^{-10}$	—	<b>1.46 (1.09-1.95)<sup>a</sup></b>	—	—	—
9q22	rs1019760	Landa et al. 2009 (76)	<b>1.47 (1.23-1.75)</b>	<b>1.65 (1.38-1.97)</b>	<b>1.56 (1.34-1.76)</b>	$1.6 \times 10^{-10}$	$9.7 \times 10^{-10}$	—	<b>2.92 (2.02-4.22)<sup>b</sup></b>	—	—	—

(Continued on the following page)



**Table 2.** Meta-analyses of published data on Caucasians with data from present GWAS (Cont'd)

Gene or locus	dbSNP ID	Reference	Published OR (allelic model)	Allelic OR (present GWAS)	Meta-analysis	$P_{\text{ass}}$	$q$	Published OR (additive model)	OR of the additive model (present GWAS)	Meta-analysis	$P_{\text{ass}}$	$q$
9q22	rs1867277	Takahashi et al. 2010 (17)	<b>1.48 (1.27-1.71)</b>	<b>1.65 (1.38-1.97)</b>	<b>1.55 (1.38-1.73)</b>	$2.9 \times 10^{-14}$	$4.9 \times 10^{-13}$	—	1.46 (1.09-1.95) <sup>a</sup>	—	—	—
		Jones et al. 2012 (75)	<b>1.75 (1.57-1.94)</b>	—	—	—	—	1.99 (1.64-2.41) <sup>a</sup>	2.92 (2.02-4.22) <sup>b</sup>	—	—	—
		Tomaz et al. 2012 (85)	<b>1.76 (1.18-2.62)</b>	—	—	—	—	3.08 (2.46-3.84) <sup>b</sup>	—	—	—	—
9q22	rs7849497	Tomaz et al. 2012 (85)	<b>2.45 (1.60-3.76)</b>	<b>1.55 (1.29-1.87)</b>	<b>1.67 (1.41-1.98)</b>	$3.2 \times 10^{-9}$	$1.4 \times 10^{-8}$	—	1.39 (1.07-1.80) <sup>a</sup>	—	—	—
		Tomaz et al. 2012 (85)	<b>1.76 (1.18-2.62)</b>	<b>1.65 (1.38-1.97)</b>	<b>1.67 (1.42-1.96)</b>	$4.4 \times 10^{-10}$	$2.2 \times 10^{-9}$	—	2.78 (1.80-4.28) <sup>b</sup>	—	—	—
		Tomaz et al. 2012 (85)	<b>2.52 (1.64-3.86)</b>	<b>1.55 (1.29-1.87)</b>	<b>1.90 (1.19-3.04)</b>	0.01	0.02	—	2.92 (2.02-4.22) <sup>b</sup>	—	—	—
9q22	rs1867280	Tomaz et al. 2012 (85)	<b>1.68 (1.13-2.49)</b>	<b>1.65 (1.38-1.97)</b>	<b>1.65 (1.41-1.95)</b>	$1.4 \times 10^{-9}$	$6.5 \times 10^{-9}$	—	1.39 (1.07-1.80) <sup>a</sup>	—	—	—
		Tomaz et al. 2012 (85)	<b>2.39 (1.56-3.67)</b>	<b>1.65 (1.38-1.97)</b>	<b>1.74 (1.48-2.05)</b>	$2.7 \times 10^{-11}$	$2.8 \times 10^{-10}$	—	1.46 (1.09-1.95) <sup>a</sup>	—	—	—
		Gudmundsson et al. 2009 (16)	<b>1.37 (1.24-1.52)</b>	<b>1.25 (1.05-1.49)</b>	<b>1.25 (1.17-1.33)</b>	0.01	0.02	—	2.92 (2.02-4.22) <sup>b</sup>	—	—	—
14q13	rs944289	Takahashi et al. 2010 (17)	1.13 (0.95-1.36)	—	—	—	—	—	1.13 (0.81-1.58) <sup>b</sup>	—	—	—
		Jones et al. 2012 (75)	<b>1.33 (1.19-1.49)</b>	—	—	—	—	—	1.48 (1.04-2.09) <sup>b</sup>	—	—	—
		Liyanarachchi et al. 2013 (82)	<b>1.25 (1.08-1.46)</b>	—	—	—	—	—	—	—	—	—
		Liyanarachchi et al. 2013 (82)	<b>1.22 (1.09-1.38)</b>	—	—	—	—	—	—	—	—	

NOTE: Meta-analyses were performed when both sources showed a  $P_{\text{ass}} < 0.2$  (arbitrary chosen in any inheritance model) or when a meta-analysis of data from the literature alone was statistically significant. Statistically significant results at a nominal level of  $P_{\text{ass}} < 0.05$  are highlighted in bold.

<sup>a</sup>Heterozygotes; <sup>b</sup>rare homozygotes; <sup>c</sup>only dominant model available.

**Table 3.** Meta-analyses between the non-Caucasian population(s) from the literature and present GWAS

Gene or locus	dbSNP ID	Reference	Published OR (allelic model)	Allelic OR (present GWAS)	Meta-analysis	$P_{\text{ass}}$	$q$	Published OR (additive model)	OR of the additive model (present GWAS)	Meta-analysis	$P_{\text{ass}}$	$q$
<b>Cell-cycle regulation and apoptosis</b>												
<i>MDM2</i>	rs2279744	Zhang et al. 2013 (36) <sup>c</sup>	<b>1.50 (1.10-2.00)</b>	1.27 (0.91-1.77)	<b>1.40 (1.12-1.74)</b>	$2.6 \times 10^{-3}$						
<i>Xenobiotic metabolism</i>												
<i>GPX3</i>	rs3792796	Lin et al. 2009 (86)	1.15 (0.90-1.46)	1.08 (0.90-1.29)	1.10 (0.96-1.27)	0.17	0.24	1.25 (0.90-1.74) <sup>a</sup> 1.19 (0.66-2.16) <sup>b</sup>	1.02 (0.78-1.33) <sup>a</sup> 1.19 (0.83-1.72) <sup>b</sup>	1.10 (0.90-1.36) <sup>a</sup> 1.19 (0.87-1.63) <sup>b</sup>	0.35 0.28	0.45 0.40
<b>Immune response and inflammation</b>												
<i>IL1RA</i>	rs1061758	Eun et al. 2012 (55)	<b>1.62 (1.14-2.28)</b>	<b>1.29 (1.02-1.65)</b>	<b>1.39 (1.14-1.70)</b>	$1.0 \times 10^{-3}$	0.01	<b>3.03 (1.52-6.06)<sup>a</sup></b> <b>3.16 (1.42-7.04)<sup>b</sup></b>	1.24 (0.94-1.64) <sup>a</sup> 1.87 (0.89-3.93) <sup>b</sup>	<b>1.41 (1.08-1.82)<sup>a</sup></b> <b>2.38 (1.38-4.11)<sup>b</sup></b>	0.01 $1.8 \times 10^{-3}$	0.09 0.02
<i>TLR6</i>	rs3775073	Kim et al. 2013 (87)	1.28 (0.91-1.81)	1.14 (0.94-1.38)	1.17 (0.99-1.38)	0.06	0.17	1.21 (0.74-1.99) <sup>a</sup> 1.67 (0.80-3.47) <sup>b</sup>	1.12 (0.86-1.44) <sup>a</sup> 1.34 (0.87-2.06) <sup>b</sup>	1.14 (0.91-1.42) <sup>a</sup> 1.42 (0.98-2.05) <sup>b</sup>	0.26 0.06	0.41 0.20
<b>Other cancer genes</b>												
<i>FOSB</i>	rs12373539	Han et al. 2012 (88)	0.79 (0.55-1.14)	0.84 (0.63-1.12)	0.82 (0.65-1.03)	0.09	0.20	0.74 (0.45-1.22) <sup>a</sup> 0.66 (0.27-1.62) <sup>b</sup>	0.84 (0.63-1.11) <sup>a</sup> 0.87 (0.39-1.91) <sup>b</sup>	0.82 (0.64-1.04) <sup>a</sup> 0.77 (0.43-1.39) <sup>b</sup>	0.10 0.39	0.18 0.46
<i>HER2</i>	rs1801200	Rebay et al. 2009 (64)	<b>1.88 (1.18-3.01)</b>	1.00 (0.79-1.28)	1.15 (0.92-1.43)	0.22	0.24	1.36 (0.78-2.37) <sup>a</sup> —	0.96 (0.73-1.26) <sup>a</sup> 1.32 (0.53-3.31) <sup>b</sup>	1.03 (0.80-1.31) <sup>a</sup> —	0.83 —	0.83 —
<i>TGFR</i>	rs2229765	Cho et al. 2012 (65)	<b>0.56 (0.39-0.80)</b>	0.94 (0.79-1.13)	<b>0.84 (0.72-0.99)</b>	0.04	0.15	<b>0.56 (0.35-0.90)<sup>a</sup></b> <b>0.28 (0.11-0.76)<sup>b</sup></b>	0.86 (0.66-1.13) <sup>a</sup> 0.94 (0.64-1.38) <sup>b</sup>	<b>0.77 (0.61-0.98)<sup>a</sup></b> 0.80 (0.56-1.15) <sup>b</sup>	0.03 0.23	0.09 0.40
<i>TTC46</i>	rs11895564	Kim et al. 2011 (67)	<b>2.04 (1.24-3.37)</b>	1.15 (0.95-1.39)	1.46 (0.84-2.54)	0.18	0.24	<b>1.96 (1.12-3.43)<sup>a</sup></b> 7.03 (0.64-78.5) <sup>b</sup>	1.01 (0.78-1.31) <sup>a</sup> 1.44 (0.96-2.18) <sup>b</sup>	1.34 (0.71-2.55) <sup>a</sup> 2.00 (0.57-7.05) <sup>b</sup>	0.37 0.28	0.45 0.40
<i>TGFB1</i>	rs2230396	Eun et al. 2013 (68)	0.90 (0.63-1.28)	0.85 (0.65-1.12)	0.87 (0.70-1.08)	0.20	0.24	0.67 (0.39-1.15) <sup>a</sup> 0.97 (0.46-2.06) <sup>b</sup>	0.78 (0.58-1.06) <sup>a</sup> 1.16 (0.43-3.17) <sup>b</sup>	<b>0.75 (0.58-0.98)<sup>a</sup></b> 1.03 (0.57-1.89) <sup>b</sup>	0.04 0.91	0.09 0.91
<i>OPN</i>	rs17524488	Mu et al. 2013 (70)	0.86 (0.71-1.05)	0.95 (0.78-1.14)	0.91 (0.76-1.04)	0.16	0.24	0.82 (0.59-1.15) <sup>a</sup> 0.74 (0.48-1.11) <sup>b</sup>	0.81 (0.63-1.04) <sup>a</sup> 1.08 (0.70-1.66) <sup>b</sup>	<b>0.81 (0.67-0.99)<sup>a</sup></b> 0.88 (0.66-1.19) <sup>b</sup>	0.04 0.41	0.09 0.46
<i>OPN</i>	rs11730582	Mu et al. 2013 (70)	<b>2.14 (1.74-2.62)</b>	1.04 (0.87-1.24)	1.49 (0.73-3.02)	0.27	0.27	<b>2.05 (1.46-2.90)<sup>a</sup></b> <b>4.31 (2.85-6.52)<sup>b</sup></b>	0.80 (0.59-1.08) <sup>a</sup> 1.08 (0.76-1.56) <sup>b</sup>	1.28 (0.51-3.21) <sup>a</sup> 2.15 (0.55-8.34) <sup>b</sup>	0.61 0.27	0.67 0.40
<i>VEGFA</i>	rs699947	Hsiao et al. 2007 (72)	<b>1.66 (1.11-2.50)</b>	1.19 (0.99-1.42)	<b>1.22 (1.05-1.41)</b>	$8.6 \times 10^{-5}$	0.05	<b>1.89 (1.08-3.32)<sup>a</sup></b> 2.30 (0.87-6.13) <sup>b</sup>	1.23 (0.94-1.63) <sup>a</sup> 1.38 (0.97-1.96) <sup>b</sup>	<b>1.26 (1.01-1.57)<sup>a</sup></b> <b>1.42 (1.04-1.94)<sup>b</sup></b>	0.04 0.03	0.09 0.15

<sup>a</sup>Heterozygotes; <sup>b</sup>rare homozygotes; <sup>c</sup>only recessive model available. Statistically significant results at a nominal level of  $P_{\text{ass}} < 0.05$  are highlighted in bold.

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(5' region near *SULF1*, OR = 1.17, 95% CI, 1.03–1.33,  $q = 0.03$ ; allelic model) were associated with increased risks (Table 2). When the meta-analyses were extended to other available populations, four more SNPs showed an evidence of association, although not significantly after FDR correction: rs2229765 (*IGF1R*, OR = 0.77, 95% CI, 0.61–0.98,  $q = 0.09$ ; heterozygotes), rs2230396 (*ITGB1*, OR = 0.75, 95% CI, 0.58–0.98,  $q = 0.09$ ; heterozygotes), rs17524488 (5' region near *OPN*, OR = 0.81, 95% CI, 0.67–0.99,  $q = 0.09$ ; heterozygotes), and rs699947 (5' region near *VEGFA*, OR = 1.22, 95% CI, 1.05–1.41,  $q = 0.05$ ; allelic model; Table 3).

#### SNPs previously studied in relation to DTC risks from genome-wide association studies or studies focused on specific intergenic regions

Genetic variants on 1p31.3, 2q35, 8p12, 9q22, and 14q13.3 were associated with DTC risk by using genome-wide approaches. Three LD blocks (defined by rs965513, rs7048394, and rs894673) on chromosome 9q22 near *FOXE1* were associated with DTC risk so far. These SNPs also showed a strong association in the present GWAS, where the allelic  $P_{\text{ass}}$  remained statistically significant also after FDR correction (Table 1). Moreover, these associations were strengthened in the meta-analyses on Caucasians in the allelic model, with OR = 1.85 (95% CI, 1.76–1.95,  $q < 10^{-20}$ ) for rs965513, OR = 1.51 (95% CI, 1.31–1.73,  $q = 2.3 \times 10^{-8}$ ) for rs7048394 and OR = 1.51 (95% CI, 1.33–1.71,  $q = 8.3 \times 10^{-10}$ ) for rs894673. Moreover, the present meta-analysis points rs334725 (1p31.3, OR = 1.32, 95% CI, 1.10–1.59,  $q = 5.1 \times 10^{-3}$ ), rs966423 (2q35, OR = 1.27, 95% CI, 1.19–1.35,  $q = 1.3 \times 10^{-12}$ ), rs2439302 (8p12, OR = 1.30, 95% CI, 1.23–1.39,  $q = 1.2 \times 10^{-15}$ ), and rs944289 (14q13, OR = 1.25, 95% CI, 1.17–1.33,  $q = 0.02$ ) as associated with the risk of DTC (Table 2).

## Discussion

Current scientists' knowledge on DTC genetic risk factors is based on a series of association studies on genes involved in different cellular mechanisms that could lead to malignant transformation of thyroid cells. Typically these studies were performed according to candidate-gene approaches, and rarely the findings were replicated using similar samples in terms of ethnicity and thyroid carcinoma histological type. Furthermore, to date, only few GWASs were performed, and a small number of genomic *loci* were associated with the risk of the disease by using this approach.

In order to gain further insights into the role of SNPs previously associated with DTC, in the present work we carefully analyzed the results of our GWAS and we performed meta-analyses with the previous studies. The associations between DTC and well-established GWAS-identified SNPs, including rs965513, rs7048394, and rs894673 near *FOXE1* (9q22), were replicated using our GWAS data. Furthermore, rs944289 near *NKX2-1* (14q13.3), rs966423 within *DIRC3* (2q35), rs334725 within *NFIA* (1p31.3), and rs2439302 within *NRG1* (8p12) showed an evidence of association in the meta-analysis of the GWAS results and previous published data. The role of these *loci* in DTC etiology was already discussed in previous works and will be not discussed here.

Although in the present work most of the SNPs assayed in previously published hypothesis-driven studies were not asso-

ciated with the risk of DTC, it is noteworthy to observe that several of them actually did associate. In particular, rs1799814 within *CYP1A1* and rs1121980 within *FTO* were replicated on our GWAS data after the application of multiple testing corrections. The meta-analysis-based approach provided an evidence of association of several additional variants, including SNPs in the DNA repair gene *HUS1* (rs2708906), cell-cycle regulation gene *WDR3* (rs4658973), xenobiotic metabolism genes *SOD1* (rs1041740, rs12626475) and *UGT2B7* (rs3924194), the immune response and inflammation genes *ALOX12* (rs1126667), *TICAM1* (rs2292151), and *IL11RA* (rs1061758), as well as other cancer genes *ATG16L1* (rs2241880), *FTO* (rs17817288, rs11642841, rs9939609), *HDAC4* (rs7584828), *IGFBP3* (rs2132572), *PIK3CA* (rs17849071), *SULF1* (rs6472462), *IGF1R* (rs2229765), *OPN* (rs17524488), and *VEGFA* (rs699947). All these SNPs were previously investigated in hypothesis-driven studies, underlying the importance of CCASs also in the era of GWAS. In particular, we highlighted the role of rs17849071 and rs17524488, whose association was not significant in previous studies but became statistically significant after increasing the sample size with the present meta-analysis. Overall, our in-depth analysis showed that some *a priori* hypotheses formulated in previous studies were confirmed and could have realistic bases for shedding some lights in the etiology of DTC. Our GWAS had an adequate statistical power to detect small size effects (>85% of power for SNPs with MAF>0.05, relative risk of 1.4 and type I error  $\alpha = 0.05$ ), that is reinforced with the data already published through the meta-analysis. However, we cannot exclude that other SNPs could be associated with DTC but failed to replicate in the present study. For example, it is worth mentioning that 13 SNPs (Supplementary Table S3) were found associated with the risk of DTC in the meta-analysis of literature data alone, although all but rs965513 were not significant in the present GWAS. Ideally, all these SNPs should be replicated in a large and independent series of cases and controls to further confirm their involvement in DTC predisposition (24). In conclusion, our findings provide additional evidence that common genetic variants have a role in DTC initiation and/or progression. Further cutting-edge studies, as novel GWASs, next-generation sequencing analysis, fine-mapping or genome-wide interactions studies, are needed to characterize all the predisposing risk factors for DTC.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

**Conception and design:** R. Elisei, C. Romei, K. Hemminki, F. Gemignani, A. Försti, S. Landi

**Development of methodology:** G. Figlioli, A. Försti

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** G. Figlioli, R. Elisei, F. Bambi, B. Chen, A. Cristaudo, K. Hemminki, A. Försti

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** G. Figlioli, R. Elisei, O. Melaiu, B. Chen, A. Köhler, K. Hemminki, A. Försti

**Writing, review, and/or revision of the manuscript:** G. Figlioli, C. Romei, M. Cipollini, A. Cristaudo, F. Gemignani, A. Försti, S. Landi

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** G. Figlioli, A. Köhler

**Study supervision:** R. Elisei, K. Hemminki, F. Gemignani, S. Landi

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# Cancer Epidemiology, Biomarkers & Prevention

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