Molecular genetics of thyroid cancer

MAHA REBAI¹ AND AHMED REBAI¹*

¹Laboratory of Molecular and Cellular Screening Processes, Centre of Biotechnology of Sfax, University of Sfax, Route Sidi Mansour, PO Box 1177, 3018 Sfax, Tunisia

(Received 9 November 2015; revised 8 March 2016; accepted 5 April 2016)

Summary

The pathogenesis of the development and progression of thyroid cancer (TC) is far from being clear at present. Accumulated evidence suggests that it is a complex polygenic disorder for which genetic factors play an important role in disease aetiology. Here we review the literature to report the genetic variations and alterations that have been described in the aetiology of TC. The functional effects of some mutations and single nucleotide polymorphisms on TC are validated, establishing the role of sequence variations in this cancer. However, large prospective studies are still required to evaluate the diagnostic and prognostic value of these genetic determinants in clinical practice.

1. Introduction

Thyroid cancer (TC) is the most prevalent endocrine malignancy having an incidence two to three times higher in women (Farahati et al., 2004). It can occur at any age although it is more frequent after the age of 30 years and significantly more aggressive in older subjects (Leenhardt et al., 2005). TC is classified into four main histology groups: papillary (PTC), follicular (FTC), medullary (MTC), and undifferentiated or anaplastic thyroid carcinomas. The great majority of malignant thyroid tumours are nonmedullary, either PTC (80–85%) or FTC (10–15%) (DeLellis et al., 2006; Kondo et al., 2006).

Molecular analysis of thyroid tumours has indicated that many genetic alterations are found to be involved in cancer development. The most affected genes are those involved in DNA repair, signal transduction and cell cycle control (Kang et al., 2002). In fact, in recent years, a multitude of genetic variations such as mutations and single nucleotide polymorphisms (SNPs) have been identified and associated with TC risk. The most frequent genetic alterations that have been described in papillary and follicular cancers, are BRAF and RAS point mutations and RET/PTC and PAX8/PPARγ rearrangements (Nikiforova & Nikiforov, 2009). Recently, it has been reported that point mutations in the TERT and TP53 genes are an important event in TC cancer diagnosis or progression (Vinagre et al., 2013; Pita et al., 2014). Yet, recent studies have demonstrated a strong association of some SNPs with TC risk. Among sequence variants that have been highly implicated in the aetiology of TC are the variants at 8q24 (rs6983267), 9q22·23 (rs965513) and 14q13·3 (rs944289, rs116909374) loci (Gudmundsson et al., 2009; 2012; Sahasrabudhe et al., 2015). These polymorphic sites may affect the enhancer activity of genes or gene regulation, but how they influence these outcomes is not precisely acknowledged.

In a complex polygenic disease such TC, which may be a result of the interaction between a number of genetic and epigenetic factors, analysis of multiple gene polymorphisms and mutations is beginning to be necessary in order to study the susceptibility of the disease. Therefore, in this report, we have reviewed the literature to describe the molecular genetics status of TC.

2. Thyroid cancer and genetic polymorphisms

Genome wide association studies (GWAS) have identified some chromosomal regions as new hotspots for TC susceptibility (Table 1 and Fig. 1). These regions are localized at 9q22·33, 14q13·3, 2q35 and 8p12. In
| SNP        | Region | Location | Gene    | Functional class | Allele risk | Sample size (cases/controls) | Population          | p-value       | OR   | Reference                                      |
|------------|--------|----------|---------|------------------|-------------|-----------------------------|---------------------|--------------|------|-----------------------------------------------|
| rs965513   | 9q22-33| 97793827 | Near FOXE1 | A                | 192/37196   | Icelandic                   | 2 × 10^{-27}          | 1.75         |      | Gudmundsson et al., 2009                     |
|            |        |          |         |                  | 90/1343     | Spanish                     | 3.0 × 10^{-10}        | 1.78         |      | Köhler et al., 2013                         |
|            |        |          |         |                  | 342/384     | Columbus                    |                     |              |      |                                               |
|            |        |          |         |                  | 2240/2218   | Italian                     |                     |              |      |                                               |
|            |        |          |         |                  | 468/470     | Polish                      |                     |              |      |                                               |
|            |        |          |         |                  | 509/1118    | UK                          |                     |              |      |                                               |
|            |        |          |         |                  | 446/420     | Spanish                     |                     |              |      |                                               |
|            |        |          |         |                  | 194/179     | Belarussian                  |                     |              |      |                                               |
|            |        |          |         |                  | 214/448     | Russian                     |                     |              |      |                                               |
| rs944289   | 14q13-3| 36180040 | Near NKX2-1 | T                | 192/37196   | Icelandic                   | 5.0 × 10^{-12}        | 1.65         |      | Takahashi et al., 2010                      |
|            |        |          |         |                  | 432/1727    | Spanish                     |                     |              |      |                                               |
|            |        |          |         |                  | 90/1343     | European                    |                     |              |      |                                               |
|            |        |          |         |                  | 342/384     | Spanish                     |                     |              |      |                                               |
| rs966423   | 2q35   | 217445617| DIRC3    | Intron           | C           | 222/24189                   | 1.0 × 10^{-9}         | 1.34         |      | Gudmundsson et al., 2012                     |
|            |        |          |         |                  | 90/1399     | Icelandic                   |                     |              |      |                                               |
|            |        |          |         |                  | 365/383     | Spanish                     |                     |              |      |                                               |
|            |        |          |         |                  | 151/832     | Columbus                    |                     |              |      |                                               |
| rs2439302  | 8p12   | 32574851 | NRG1     | Intron           | G           | 222/24189                   | 2.0 × 10^{-9}         | 1.36         |      | Gudmundsson et al., 2012                     |
|            |        |          |         |                  | 90/1399     | Icelandic                   |                     |              |      |                                               |
|            |        |          |         |                  | 365/383     | Spanish                     |                     |              |      |                                               |
|            |        |          |         |                  | 151/832     | Columbus                    |                     |              |      |                                               |
| rs116909374| 14q13-3| 36269155 | MBIP     | T                | 222/24189   | Icelandic                   | 5.0 × 10^{-11}        | 2.09         |      | Gudmundsson et al., 2012                     |
|            |        |          |         |                  | 90/1399     | Spanish                     |                     |              |      |                                               |
|            |        |          |         |                  | 365/383     | Columbus                    |                     |              |      |                                               |
| rs6759952  | 2q35   | 217406996| DIRC3    | Intron           | T           | 2240/2218                   | 6.0 × 10^{-10}        | 1.25         |      | Köhler et al., 2013                         |
|            |        |          |         |                  | 468/470     | Italian                     |                     |              |      |                                               |
|            |        |          |         |                  | 509/1118    | Polish                      |                     |              |      |                                               |
|            |        |          |         |                  | 446/420     | Spanish                     |                     |              |      |                                               |
that the variant rs1867277 affects FOXE1 transcription. In fact, it has been reported that the A allele of this SNP increases the transcriptional activity of the FOXE1 gene promoter, by the recruitment of leucine zipper upstream stimulatory factors 1 and 2 (Landa et al., 2009). Regarding the FOXE1 polyAla tract, it has been reported that it has 11–22 alanine residues, although FOXE1 14Ala and FOXE1 16Ala account for greater than 98% of reported alleles (Kallel et al., 2010). Some studies have suggested a functional consequence for the presence of polyAla expansions (>14) but not for contractions (≤14). FOXE1 with 16Ala induced a stronger transactivation of the thyroglobulin promoter than the 14Ala variant (Carré et al., 2007). However, a recent study has reported a modest transcriptional impairment of 16Ala FOXE1, when compared with the function of the 14Ala variant, on FOXE1 responsive promoters, which was not attributable to differences in DNA binding (Liyanarachchi et al., 2013).

(ii) RET

The rearranged during transfection (RET) proto-oncogene is one of the receptor tyrosine kinase, cell-surface molecules that transduce signals for cell growth and differentiation. A wide panel of SNPs in the RET gene have been reported to the curated databases but only a limited, and perhaps selected, number of these RET variants have been tested for an association (Table S1). Among them are the nonsynonymous variant G691S (rs1799939) in exon 11, the synonymous variants L769L (rs1800861) in exon 13, S836S (rs1800862) in exon 14 and S904S (rs1800863) in exon 15. These SNPs have been repeatedly implicated in the increase of MTC risk (Figlioli et al., 2013; Lantieri et al., 2013). However, the effect of RET polymorphisms on other types of TC remains unclarified. Only the SNP S836S was positively correlated with PTC but not with FTC. Despite the presence of some studies suggesting a possible role of the RET polymorphisms in MTC susceptibility, the data about the true association between MTC and RET variants were conflicting and extremely variable. The cause of this incoherence has been assigned to the limited number of patients enrolled (underpowered studies) and/or to the genetic variability among different populations (Weber & Eng, 2005; Fugazzola et al., 2008). To avoid this high discrepancy in observed data, Weber & Eng (2005) in their study have suggested the application of rigorous parameters to dissect out the few true RET modifiers among a vast amount of random associations and proposed an approach termed reverse phenotyping. Here, the genotype/haplotype is identified in a cohort study and then associated with phenotypical factors, analogous to an unsupervised analysis used in global gene

(i) FOXE1

Forkhead box E1 (FOXE1) is a single exon gene located at chromosome 9q22.33 encoding the transcription factor FOXE1 (or TTF-2), which likely plays a crucial role in thyroid morphogenesis. This transcription factor regulates thyroglobulin and thyroid peroxidase expression. Many association studies have been performed to investigate the role of FOXE1 polymorphisms in TC susceptibility. Several variants of this gene have been positively correlated with thyroid malignancy (Table S1). However, two common variations (rs1867277 and rs71369530) have been associated with TC risk in various ethnic groups (Matsuse et al., 2011; Gudmundsson et al., 2012; Jones et al., 2012).

The SNP rs1867277 is caused by an A/G transition in the 5'UTR region of the gene, whereas the rs71369530 polymorphism is a polymorphic polyalanine tract (rs71369530, polyAla) just distal to its DNA-binding domain. Recently, it has been shown
expression analysis that avoids assumptions based on the phenotype to identify hidden patterns.

On the other hand, it has been shown that a synonymous polymorphism in exon 2 (Ala45Ala, rs1800858), which occurred at a lower frequency among cases of MTC, may confer a protective allele against the development of MTC (Cebrian et al., 2005). However, a recent study has shown that the G allele of this SNP remarkably increases the risk of TC (Huang & Yang, 2015). The mechanism by which the silent polymorphisms may act in the development of TC may include transcript stability, mRNA structure, and DNA protein binding and protein folding (Ho et al., 2005). In the case of the nonsynonymous SNP G691S, the two amino acids, glycine in the wild-type RET protein and serine in the polymorphic RET variant, confer different electrochemical and conformational structures to the RET protein, and consequently influence the processing, folding, subcellular localization or function of the protein (Robledo et al., 2003). More recently, the functional activity of this variant has been investigated by western blot analyses and the result has showed that the fraction of Ret9-G691S protein located at the plasma membrane level was overrepresented when compared to Ret9-WT, suggesting facilitated targeting at the cell membrane for this variant (Fugazzola et al., 2008).

The relationship between the RET variants and the clinicopathological features of the disease is, yet, unclarified. In the study of Ceolin et al. (2012), no significant correlation has been observed between the RET variants analysed (G691S, L769L, S836S and S904S) and the clinicopathological parameters of the patients. Nevertheless, patients carrying haplotypes with three or four risk alleles had increased risk for lymph node and distant metastases at diagnosis. More recently, two RET SNPs (G691S and S904S) have been significantly associated with an increase in tumour size at diagnosis and a more aggressive disease (Santos et al., 2014).

(iii) XRCCI

The X-ray repair complementing group 1 (XRCCI) gene encodes a scaffold protein involved in the repair of DNA single-strand breaks formed by ionizing radiation and alkylation damage. Numerous validated SNPs in the XRCCI gene have been identified, only three of which were most widely investigated including Arg194Trp on exon 6 (rs1799782, C/T), Arg280His on exon 9 (rs25489, G/A) and Arg399Gln on exon 10 (rs25487, G/A; Table S1). Over the last decade, several epidemiological studies have reported the association regarding XRCCI polymorphisms and TC risk (Fard-Esfahani et al., 2011; Ryu et al., 2011; Santos et al., 2012). However, a significant heterogeneity among studies has been observed. In fact, increased risks for DTC have been shown for Arg194Trp and Arg280His genotypes while a mild reduction of risk has been estimated for the Arg399Gln polymorphism (Fard-Esfahani et al., 2011). Nevertheless, it has been suggested in a meta-analysis involving eight different populations that the Arg399Gln polymorphism may be associated with decreased TC risk among the Caucasian population while the Arg194Trp SNP may be associated with a tendency of increased TC risk in the two larger sample size trials. But, no significant association has been found between the Arg280His polymorphism and TC (Qian et al., 2012). On the other hand, in a more recent study only the Arg194Trp SNP has been associated with increased risk of TC (Wang et al., 2015).

It has been suggested that the functional significance of the Arg194Trp polymorphism is due to its location in an evolutionarily conserved region, and the occurrence of chromosomal breaks is largely increased among cases with the Arg/Arg genotype (Voelckner et al., 2007). For the Arg399Gln polymorphism, which is located with a relatively nonconserved region between conserved residues of the BRCA1 COOH terminus domain, it may be associated with higher sister chromatid exchange frequency and prolonged cell cycle delay in response to ionizing radiation (Hu et al., 2001; Matullo et al., 2006).

Although in the same gene, these two different SNPs may exert influence on the XRCCI activity in different ways, thus they might have different effects on cancer risk. Regarding the Arg280His polymorphism, which is located in the PCNA-binding region of the XRCCI protein, it has been suggested that this variant could potentially alter the structure of XRCCI and its ability to interact with apurinic/apyrimidinic endonuclease (Yan et al., 2009).

(iv) Other genomic regions

(a) 8q24

SNPs in the 8q24 chromosomal gene-poor region, known as the ‘gene desert’, have been consistently implicated in GWAS as susceptibility loci for several cancer sites including TC (Neta et al., 2012). Most of these SNPs are located in the area known as cancer susceptibility candidate 8 (CASC8; Table S1). Among the important SNPs of the 8q24 chromosomal region, there is the SNP rs6983267 which has been identified as a multi-cancer SNP. This polymorphic site has been investigated in a large and multi-ethnic study and the results showed a significant association between the rs6983267 G allele and TC. In fact, it has been suggested that this variant increases disease risk by ~13% (Saharsrabudhe et al., 2015). However, the precise function of this locus is still under investigation.
Genetics of thyroid cancer

(b) Near FOXE1 (9q22-33)
Since it has been shown that the SNP rs965513 (located 57 kb upstream of the FOXE1 gene on chromosome 9q22) was a new hot spot for TC susceptibility (Gudmundsson et al., 2009; 2012), the relationship between this polymorphic site and TC risk has been independently replicated by subsequent studies (Wang et al., 2013). It has been suggested to tag a functional variation near the FOXE1 gene that contributes to an increased risk of developing TC. Besides, the variant has also been associated with low serum concentrations of thyroid stimulating hormone, and free thyroxin (Gudmundsson et al., 2012). More recently, a significant correlation has been observed between this polymorphic site and more aggressive disease (advanced stage) (Penna-Martinez et al., 2014).

(c) 14q13
Among sequence variants that have been highly implicated in the aetiology of TC are the SNPs rs944289 and rs116909374, located on 14q13 in regions containing no annotated genes. These two polymorphic sites are located within two distinct but neighbouring linkage disequilibrium regions and have been associated with low serum concentrations of thyroid stimulating hormone, and free thyroxin (Gudmundsson et al., 2012). More recently, a significant correlation has been observed between this polymorphic site and more aggressive disease (advanced stage) (Penna-Martinez et al., 2014).

3. Thyroid cancer and gene mutations
Mutation phenomenon is a rare event in TC compared to other types of malignancies where the mean percentage of mutations does not exceed one mutation per mega base. The signatures of mutational processes (mutational processes that leave idiosyncratic patterns of mutations) have been attributed mostly to unknown aetiologies (about 80%); however, the CpG deamination and off-target modification of DNA by the APOBEC proteins have also been involved but with relatively low frequencies (Martincorenna & Campbell, 2015). According to the COSMIC database (COSMIC database, 2015) and the Cancer Gene Census database (www.sanger.ac.uk/CGP/Census), few genes across the recurrently mutated cancer genes (79 genes among 198 genes in mutated cancer genes) have been affected by somatic mutations (non-synonymous coding substitution or small insertion deletion) and the most affected gene was the BRAF gene (Martincorenna & Campbell, 2015).

Of the several mutations that have been found in TC, only few have characterized TC (Fig. 1). These mutations have affected genes involved in cell proliferation, protein synthesis and cell survival pathways, including rearrangements of RET/PTC and PAX8/PPARγ, activating point mutations in BRAF serine/threonine kinase, in the RAS proto-oncogenes, in the TERT gene or inactivating mutations in the tumour suppressors gene TP53 (Table 2).

(i) BRAF
The BRAF proto-oncogene, a serine/threonine kinase, encodes a protein belonging to the raf/mil family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERK signalling pathway, which affects cell division, differentiation and secretion. Mutations in this gene are the most common genetic event in PTC. About 40 mutations have been identified in human thyroid tumours (COSMIC database, 2015) most of which are missense substitutions (36-8%). Most oncogenic BRAF mutations are located in the glycine-rich P loop (residues 462–471) and activation segment (residues 593–622) (Wan et al., 2004; Michaloglou et al., 2008).

The Glu586Lys, Val600Glu, Val600Asp, Val600Lys, Val600Arg and Lys601Glu mutations have been classified as a high kinase activity group, while nine other mutations, Gly464Glu, Gly464Val, Gly466Ala, Gly469Glu, Asn581Ser, Phe595Leu, Leu597Val, Leu597Arg and Thr599Ile, have been classified as an intermediate kinase activity group. However, four mutations, Gly466Glu, Gly466Val, Gly596Arg and Asp594Val, have lower kinase activity than basal wild-type BRAF activity (Wan et al., 2004; Michaloglou et al., 2008). The BRAF Val600 mutations mimic phosphorylation of Thr599/Ser602 (required for the activation of wild-type BRAF) and destabilize interactions between residues within the hydrogen bond network in BRAF, rendering the BRAF constitutively active (Michaloglou et al., 2008; Fratev & Jonsdottir, 2009).

Over 90% of BRAF mutations are T1799A, resulting in a substitution of glutamine for valine at amino acid codon 600 (Val600Glu, BRAFV600E), while other BRAF mutations are rarely reported. It has been shown that BRAFV600E leads to expression of a constitutively active kinase BRAF and was associated with aggressive clinicopathological characteristics (such as extrathyroidal invasion, lymph node metastasis and advanced tumour stage) (Lee et al., 2009; Lin et al., 2010), high tumour recurrence even with low stage disease (Xing et al., 2005) as well as radioiodine treatment failure in PTC (Mian et al., 2008) and high tumour related mortality (Elisei...
et al. 2008). More recently, the \(BRAF^{V600E}\) mutation has been investigated in a large cohort of PTC and it has been suggested that this genetic alteration represents a diverse group of tumours, consisting of at least four molecular subtypes, with varying degrees of thyroid differentiation. In this study, \(BRAF^{V600E}\) has been associated with less-differentiated tumours enriched for classical and tall cell histology, and with distinct gene expression and DNA methylation patterns (Cancer Genome Atlas Research Network, 2014).

\(BRAF\) fusions have been identified in PTC (2.7%) with diverse gene patterns including \(SND1\) (0-6%) and \(MKRN1\) (0.2%). Some of these fusions supported \(BRAF\) signalling with expression and conservation of its kinase domain (\(MKRN1/BR\), while others suggested an alternative activating mechanism (Cancer Genome Atlas Research Network, 2014).

(ii) \(RET\)

The \(RET\) proto-oncogene has been involved in the oncogenesis of medullary and papillary thyroid carcinomas by activation of tyrosine kinases either by point mutation or rearrangement.

There are now at least 30 types of \(RET/PTC\) rearrangements involving \(RET\) and 10 different genes. \(RET/PTC1\) (fusion \(CCDC6\) and \(RET\)) and \(RET/PTC3\) (fusion \(NCOA4\) and \(RET\)) are by far the most common rearrangements (COSMIC database, 2015). All of the rearrangements are due to DNA damage and result in the fusion of the \(RET\) tyrosine kinase domain to the 5'-terminal region of heterologous genes. \(RET/PTC\) rearrangements are very common in radiation-induced tumours but have been detected in variable proportions of sporadic (non-radiation associated) papillary carcinomas. Little is known about the clinical and pathologic features of the tumours featuring \(RET/PTC\) rearrangements. Several reports have failed to show correlation of \(RET/PTC\) rearrangements with clinicopathological markers of increased morbidity (Soares et al., 1998; Tallini et al., 1998). However, \(RET/PTC1\) and \(RET/PTC3\) have been associated with less and more aggressive tumours, respectively (Nikiforov et al., 1997; Tallini et al., 1998). A recent study performed on PTC has shown that chromosomal rearrangements including \(RET\) fusions are associated with younger age at diagnosis but not with risk of recurrence (Cancer Genome Atlas Research Network, 2014).

Activating somatic mutations in the \(RET\) proto-oncogene have been found in sporadic MTC with a frequency ranging from 23 to 69% of patients' tumours. The most frequent somatic mutation is Met918Thr in exon 16 (COSMIC database, 2015). This mutation has been involved in the initial event of the development of MTC and has a poor prognosis (Zedenius et al., 1995; Romei et al., 1996). Some other somatic missense point mutations as well as small oligonucleotide deletions or insertions in exons 10, 11, 13 and 15 have also been reported in sporadic MTC tumours but with a considerably lower frequency (Marsh et al., 1996; Alemi et al., 1997; Kalinin & Frilling, 1998; Uchino et al., 1999; Bugalho et al., 2000).

(iii) \(RAS\)

\(RAS\) family proteins are small GTPases that play a role in cellular growth, differentiation, adhesion and migration. \(RAS\) mutations are among the most common genetic alterations that have been observed in thyroid tumours and that lead to constitutive activation of the \(RAS\) proteins. Recent studies have reported that 10–20% of PTC and 40–50% of FTC harbour \(RAS\) mutations (Nikiforova et al., 2003; Nikiforov, 2008; Nikiforov & Nikiforova, 2011). They have been associated with higher malignancy, poor prognoses, distant metastasis and shorter overall survival rate in poorly differentiated thyroid carcinomas (Garcia-Rostan et al., 2003; Volante et al., 2009). \(RAS\) mutations have also been reported in MTC (25%) and constitute a frequent molecular event in \(RET\)-negative sporadic MTC (Nikiforov & Nikiforova, 2011). However, their role in MTC tumorigenesis remains unclear (Oczko-Wojciechowska et al., 2015).

In the Cancer Genome Atlas project result (Cancer Genome Atlas Research Network, 2014), \(RAS\) mutations have been identified as driver mutations for PTC and have been significantly associated with highly
differentiated tumours enriched for follicular histology and low risk of recurrence.

The RAS genes consist of three families: NRAS, HRAS and K Ras. RAS point mutations mostly occur in codons 12, 13 and 61 (exons 2 and 3) (Lee et al., 2013). The NRAS mutation at codon 61 (exon 3) accounted for 67–88% of all RAS mutations (Vasko et al., 2003).

(iv) PAX8/PPARγ

PAX8/PPARγ is formed through the translocation t(2;3)(q13;p25) that fuses the promoter and 5′-coding portion of the thyroid-specific transcription factor PAX8 gene to the full-length coding sequence of the nuclear receptor peroxisome proliferator-activated receptor-gamma 1 gene (Kroll et al., 2000).

PAX8/PPARγ was presumed to be specific for FTC (Kroll et al., 2000). Subsequent studies have confirmed PAX8/PPARγ presence in 30–40% of FTC and also found it in 2–13% of follicular adenomas (Dwight et al., 2003; French et al., 2003; Nikiforova et al., 2003). Additional studies have reported the occurrence of PAX8/PPARγ rearrangement in the follicular variant of PTC, typically with low frequency (1–5%) and have reported occurrence occasionally in PTC (1–1%) (Armstrong et al., 2014; Cancer Genome Atlas Research Network, 2014). The clinical course of the PAX8/PPARγ rearrangement has been indolent and the disease free survival was near 100% at 5 years (Yip et al., 2015).

(v) TERT

Telomerase reverse transcriptase (TERT) is a ribonucleoprotein polymerase that maintains telomere repeat TTAGGG at the ends of chromosomes and consists of a protein component with reverse transcriptase activity and a RNA component that serves as a template (Harrington et al., 1997). Recently, highly frequent mutations in the promoter region of TERT have been reported in many malignancies including TC (Horn et al., 2013; Huang et al., 2013; Killela et al., 2013; Vinagre et al., 2013). These mutations occur in two hot spot positions, located at -124 bp and -146 bp upstream from the ATG start site and confer enhanced TERT promoter activity putatively by generating a consensus binding site (GGAA) for E-26 transcription factors within the TERT promoter region (Huang et al., 2013). In the Cancer Genome Atlas Project results, TERT mutations have been identified in 9.4% of the informative papillary tumours with 7% for C228T, 0.3% for C228A and 2.1% for C250T substitutions (Cancer Genome Atlas Research Network, 2014).

TERT promoter mutations are an indicator of clinically aggressive tumours. In fact, these mutations have been significantly associated with distant metastases, higher stage and persistent disease. Patients with DTC harbouring TERT promoter mutations have been submitted to more radiiodine treatments with higher cumulative dose and to more treatment modalities (Melo et al., 2014). Also, TERT mutations have been correlated with disease specific mortality (Melo et al., 2014). These associations were consistent with the published results of the Cancer Genome Atlas Research Project, where TERT mutations have been associated with older age as well as higher risk of recurrence and it has been suggested that these mutations may be used to identify high risk patients (Cancer Genome Atlas Research Network, 2014). Recently, it has been shown that the prognostic value of TERT mutations is significantly stronger than that of BRAFV600E (Muzza et al., 2015).

(vi) TP53

Tumour suppressor protein (TP53) is a transcription factor that regulates the expression of target genes in response to diverse cellular stresses, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair or changes in metabolism. Mutations in the TP53 gene are a rare event in well DTC (PTC and FTC), while they are frequent in more advanced forms of carcinoma. In fact, TP53 mutations are a major event in poor DTC and anaplastic TC having a prevalence of 27 and 48%, respectively (Guerra et al., 2013; Pita et al., 2014). Virtually, all the mutations that have been reported are located in the hot spot region located between exons 5 and 9, where codon 273 is the one that is more often affected (Donghi et al., 1993; Fagin et al., 1993).

4. Conclusion

In summary, the genetic predisposition of TC has been highlighted in several studies. Numerous mutations and polymorphisms have been associated with this type of malignancy. The most affected genes are those involved in DNA repair, signal transduction and cell cycle control. Also, the importance of some genetic elements located on gene-poor regions was highlighted. These and other emerging molecular markers may provide additional approaches to thyroid tumour classification (such as suggested in the Cancer Genome Atlas Project), and may stimulate the development of novel approaches to tumour diagnosis and additional parameters for prognostic assessment as well as potential biologic therapeutic strategies. However, large prospective studies are required to further evaluate the diagnostic and prognostic power of these genetic elements.

This work was supported by the Ministry of Higher Education and Scientific Research, Tunisia.
Declaration of interest
None.

Supplementary material
The online supplementary material can be found available at http://dx.doi.org/10.1017/S0016672316000057

References
Alemi, M., Lucas, S. D., Sallstrom, J. F., Bergholm, U., Akerstrom, G. & Wilander, E. (1997). A complex nine base pair deletion in RET exon 11 common in sporadic medullary thyroid carcinoma. Oncogene 14, 2041–2045.
Armstrong, M. J., Yang, H., Yip, L., Ohori, N. P., McCoy, K. L., Stang, M. T., Hodak, S. P., Nikiforova, M. N., Carty, S. E. & Nikiforov, Y. E. (2014). PAX8/PPARγ re-arrangement in thyroid nodules predicts follicular-pattern carcinomas, in particular the encapsulated follicular variant of papillary carcinoma. Thyroid 24(9), 1369–1374.
Bugalho, M. J., Coelho, I. & Sobrinho, L. G. (2000). Somatic trinucleotide change encompassing codons 882 and 883 of the RET proto-oncogene in a patient with sporadic medullary thyroid carcinoma. European Journal of Endocrinology 142, 573–575.
Cancer Genome Atlas Research Network (2014). Integrated genomic characterization of papillary thyroid carcinoma. Cell 159(3), 676–690.
Carré, A., Castanet, M., Sura-Trueba, S., Ghezzi, G., Van Vliet, G., Trochet, D., Amiel, J., Léger, J., Czernichow, P., Scotet, V. & Polak, M. (2007). Polymorphic length variation in the pair cross-complementing group 1 gene and risk of differentiated thyroid carcinoma in Iran. Iranian Biomedical Journal 15, 73–78.
Frigioli, G., Landi, S., Romei, C., Elisei, R. & Gemignani, F. (2013). Medullary thyroid carcinoma (MTC) and RET proto-oncogene: mutation spectrum in the familial and sporadic forms and a meta-analysis of studies on the sporadic form. Mutation Research 752, 36–44.
Frate, F. P. & Jonsdottir, S. O. (2009). An in silico study of the molecular basis of B-RAF activation and conformational stability. BMC Structural Biology 9, 47.
French, C. A., Alexander, E. K., Cibas, E. S., Nose, V., Laguette, J., Faquin, W., Garber, J., Moore, F., Fletcher, J. A., Larsen, P. R. & Kroll, T. G. (2003). Genetic and biological subgroups of low-stage follicular thyroid cancer. American Journal of Pathology 162, 1053–1060.
Fugazzola, L., Muzza, M., Mian, C., Cordella, D., Barollo, S., Alberiti, L., Cirello, V., Dazzi, D., Girelli, M. E., Opocher, G., Beck-Peccoz, P. & Persani, L. (2008). A composite panel of RET genotypes in sporadic medullary thyroid cancer: studies in a large Italian series. Clinical Endocrinology 69(3), 418–425.
García-Rostan, G., Zhao, H., Camp, R. L., Pollan, M., Herrero, A., Pardo, J., Wu, R., Carcangiu, M. L., Costa, J. & Tallini, G. (2013). Ras mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer. Journal of Clinical Oncology 31(17), 2326–2335.
Gudmundsson, J., Sulem, P., Gudjardarsson, D. F., Jonassson, J. G., Masson, G., He, H., Jonasdottir, A., Sigurdsson, A., Stacey, S. N., Johannsdottir, H., Helgadottir, H., Li, W., Nagy, R., Ringel, M. D., Kloos, R. T., de Visser, M. C., Plantinga, T. S., den Heijer, M., Aguillo, E., Panadero, A., Prats, E., Garcia-Castaño, A., De Juan, A., Rivera, F., Walters, G. B., Bjarnason, H., Tryggvadottir, L., Eyjolfsson, G. I., Bjornsardottir, U. S., Holm, H., Olfsson, I., Kristjansson, K., Kristinsson, H., Magnusson, O. T., Thorleifsson, G., Gulcher, J. R., Kong, A., Kim, Y. A., Jonsson, T., Hjartarson, H., Mayordomo, J. I., Netea-Maier, R. T., de la Chapelle, A., Hrafnikelsson, J., Thorsteindottir, U., Rafnar, T. & Stefansson, K. (2012). Discovery of common variants associated with low TSH levels and thyroid cancer risk. Nature Genetics 44, 319–322.
Gudmundsson, J., Sulem, P., Gudjardarsson, D. F., Jonassson, J. G., Sigurdsson, A., Bergthorsson, J. T., He, A., Ogulini, C., Viola, D., Lupi, C., Biagini, A., Giannini, R., Romei, C., Miccoli, P., Pinchera, A. & Basolo, F. (2008). BRAF (V600E) mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. Journal of Clinical Endocrinology and Metabolism 93(10), 3943–3949.
Fagin, J. A., Matsuo, K., Karmakar, A., Chen, D. L., Tang, S. H. & Koehler, H. P. (1993). High prevalence of mutations of the p53 gene in poorly differentiated human thyroid carcinomas. Journal of Clinical Investigation 91(1), 179–184.
Farahati, J., Geling, M., Mader, U., Mortl, M., Luster, M., Muller, J. G., Flentje, M. & Reiners, C. (2004). Changing trends of incidence and prognosis of thyroid carcinoma in lower Franconia, Germany, from 1981–1995. Thyroid 14, 141–147.
Fard-Esfahani, P., Fard-Esfahani, A., Fayaz, S., Ghanbarzadeh, B., Saidi, P., Mohabati, R., Bidoki, S. K. & Majdi, M. (2011). Association of Arg194Trp, Arg280His and Arg399Gln polymorphisms in X-ray repair cross-complementing group 1 gene and risk of differentiated thyroid carcinoma in Iran. Iranian Biomedical Journal 15, 73–78.
H., Blondal, T., Geller, F., Jakobsdottir, M., Magnusdottir, D. N., Matthiasdottir, S., Stacey, S. N., Skarphedinsson, O. B., Helgadottir, H., Li, W., Nagy, R., Aguilo, E., Faure, E., Prats, E., Saez, B., Martinez, M., Eyiolfsson, G. I., Bjornsdottir, U. S., Holm, H., Kristjansson, K., Frigge, M. L., Kristvinsson, H., Gulcher, J. R., Jonsson, T., Rafnar, T., Hjartarson, H., Mayordomo, J. I., de la Chapelle, A., Hrafniksson, J., Thorsteinsson, D., Kong, A. & Stefansson, K. (2009). Common variants on 9q22.33 and 14q13-3 predispose to thyroid cancer in European populations. Nature Genetics 41, 460–464.

Guerra, A., Di Crescenzo, V., Garzi, A., Cinelli, M., Carlomagno, C., Tonaccheri, M., Zeppa, P. & Vitale, M. (2013). Genetic mutations in the treatment of anaplastic thyroid cancer: a systematic review. BMC Surgery 13, S44.

Harrington, L., McPhail, T., Mar, V., Zhou, W., Oulton, R., Bass, M. B., Arruda, I. & Robinson, M. O. (1997). A mammalian telomerase-associated protein. Science 275, 973–977.

Ho, T., Li, G., Zhao, C., Wei, Q. & Sтургис, Е. М. (2005). RET polymorphisms and haplotypes and risk of differentiated thyroid cancer. Laryngoscope 115, 1035–1041.

Horn, S., Figil, A., Rachakonda, P. S., Fischer, C., Sucker, A., Gast, A., Kadel, S., Moll, I., Nagore, E., Hemminki, K., Schadendorf, D. & Kumar, R. (2013). TERT promoter mutations in familial and sporadic melanoma. Science 339, 959–961.

Hu, J. J., Smith, T. R., Miller, M. S., Mohrenweiser, H. W., Golden, A. & Case, I. D. (2001). Amino acid substitution variants of APE1 and XRCC1 genes associated with ionizing radiation sensitivity. Carcinogenesis 22(6), 917–922.

Huang, F. W., Hodis, E., Xu, M. J., Kryukov, G. V., Chinn, L. & Garraway, L. A. (2013). Highly recurrent TERT promoter mutations in human melanoma. Science 339, 957–959.

Huang, R. X. & Yang, F. (2015). RET polymorphisms might be the risk factors for thyroid cancer. International Journal of Clinical and Experimental Pathology 8(5), 5793–5797.

Jendrzejewski, J., He, H., Radomska, H. S., Li, W., Nagy, R., Aguilo, E., Faure, E., Prats, E., Saez, B., Martinez, M., Eyiolfsson, G. I., Bjornsdottir, U. S., Holm, H., Kristjansson, K., Frigge, M. L., Kristvinsson, H., Gulcher, J. R., Jonsson, T., Rafnar, T., Hjartarson, H., Mayordomo, J. I., de la Chapelle, A., Hrafniksson, J., Thorsteinssdottr, U., Kong, A. & Stefansson, K. (2009). Common variants on 9q22.33 and 14q13–3 predispose to thyroid cancer in European populations. Nature Genetics 41, 460–464.

Kang, H. J., Kim, S. W., Kim, H. J., Ahn, S. J., Bae, J. Y., Park, S. K., Kang, D., Hirvonen, A., Choe, K. J. & Noh, D. Y. (2002). Polymorphisms in the estrogen receptor-alpha gene and breast cancer risk. Cancer Letters 178, 175–180.

Killela, P. J., Reitman, Z. J., Jiao, Y., Bettegowda, C., Agrawal, N., Diaz, L. A., Friedman, A. H., Friedman, H., Gallia, G. L., Giovannella, B. C., Grollman, A. P., He, T. C., He, Y., Hruban, R. H., Jallo, G. I., Mandahl, N., Meeker, A. K., Mertens, F., Netto, G. J., Rasheed, B. A., Riggins, G. J., Rosenquist, T. A., Schiffman, M., Shih, I. M., Theodoreescu, D., Torbenson, M. S., Velculescu, V. E., Wang, T. L., Wentzensen, N., Wood, L. D., Zhang, M., McLendon, R. E., Bigner, D. D., Kinzler, K. W., Vogelstein, B., Papadopoulos, N. & Yan, H. (2013). TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proceedings of the National Academy of Sciences of the United States of America 110, 6021–6026.

Köhler, A., Chen, B., Gemignani, F., Elisei, R., Romei, C., Figlioli, G., Cipollini, M., Cristaudo, A., Bambi, F., Hoffmann, P., Herms, S., Kalemba, M., Kula, D., Harris, S., Broderick, P., Houlston, R., Pastor, S., Marcos, R., Velázquez, A., Jarzab, B., Hemminki, K., Landi, S. & Försti, A. (2013). Genome-wide association study on differentiated thyroid cancer. Journal of Clinical Endocrinology and Metabolism 98(10), E1674–E1681.

Kondo, T., Ezzat, S. & Asa, S. L. (2006). Pathogenetic mechanisms in thyroid follicular-cell neoplasia. Nature Reviews Cancer 6, 292–306.

Kroll, T. G., Sarraf, P., Pecciarini, L., Chen, C. J., Mueller, E., Spiegelman, B. M. & Fletcher, J. A. (2000). PAX8-PPARgamma1 fusion oncogene in human thyroid carcinoma [corrected]. Science 289, 1357–1360.

Landa, I., Ruiz-Llorente, S., Montero-Conde, C., Ingлада-Pérez, L., Schiavi, F., Leskil€€, S., Pita, G., Milne, R., Maravall, J., Ramos, J. A., Andia, V., Rodriguez-Poyo, P., Jara-Albarr€€, A., Meoro, A., del Peso, C., Arribas, L., Iglesias, P., Caballero, J., Serrano, J., Picó, A., Pomares, F., Giménez, G., Lope€€-Mondejar, P., Castello, R., Merante-Boschin, I., Pelizzo, M. R., Mauricio, D., Opocher, G., Rodriguez-Antona, C., González-Neira, A., Matías-Guiu, X., Santisteaban, P. & Robledo, M. (2009). The variant rs1867277 in FOXE1 gene confers thyroid cancer susceptibility through the recruitment of USF1/USF2 transcription factors. PLoS Genetics 5(9), e1000637.

Lantieri, F., Caroli, F., Ceccherini, I. & Griseri, P. (2013). The involvement of the RET variant G691S in medullary thyroid carcinoma enlightened by a meta-analysis study. International Journal of Cancer 132, 2808–2819.

Lee, S. R., Jung, C. K., Kim, T. E., Bae, J. S., Jung, S. L., Choi, Y. J. & Kang, C. S. (2013). Molecular genotyping of follicular variant of papillary thyroid carcinoma correlates with diagnostic category of fine-needle aspiration cytology: values of RAS mutation testing. Thyroid 23(11), 1416–1422.

Lee, X., Gao, M., Ji, Y., Yu, Y., Feng, Y., Li, Y., Zhang, Y., Cheng, W. & Zhao, W. (2009). Analysis of differential BRAF(V600E) mutational status in high aggressive papillary thyroid microcarcinoma. Annals of Surgical Oncology 16, 240–245.

Leenhardt, L., Ménégax, F., Franc, B., Hoang, C., Sulem, S., Bernier, M. O., Dupasquier-Fédiaysvky, L., Le Marois, E., Rouxel, A., Chigot, J. P., Chérié-Challine, L. & Aurengo, A. (2005). Cancers de la thyroïde. EM consulte. Available from https://www.cambridge.org/core/core. IP address: 207.241.231.83, on 04 May 2019 at 14:58:30, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. doi:10.1017/S0016672316000057
at www.em-consulte.com/article/29159/cancers-de-la-thyroid.

Lin, K. L., Wang, O. C., Zhang, X. H., Dai, X. X., Hu, X. Q. & Qu, J. M. (2010). The BRAF mutation is predictive of aggressive clinicopathological characteristics in papillary thyroid microcarcinoma. *Annals of Surgical Oncology* 17, 3294–3300.

Liyanarachchi, S., Wojcicka, A., Li, W., Czetwertynska, M., Matullo, G., Dunning, A. M., Guarrera, S., Baynes, C., Melo, M., da Rocha, A. G., Vinagre, J., Batista, R., Peixoto, M., Matsuse, M., Takahashi, M., Mitsutake, N., Nishihara, E., Michaloglou, C., Vredeveld, L. C., Mooi, W. J. & Peeper, M. (2015). Telomerase in differentiated thyroid cancer. *Molecular and Cellular Endocrinology* 399, 288–295.

Neta, G., Yu, C. L., Brenner, A., Gu, F., Hutchinson, A., Pfeifer, R., Sturgis, E. M., Xi, L., Linet, M. S., Alexander, B. H., Chanock, S. & Sigurdson, A. J. (2012). Common genetic variants in the 8q24 region and risk of papillary thyroid cancer. *Laryngoscope* 122(5), 1040–1042.

Nikiforov, Y. E. & Nikiforova, M. N. (2011). Molecular genetics and diagnosis of thyroid cancer. *Nature Reviews Endocrinology* 7, 569–580.

Nikiforov, Y. E. (2008). Thyroid carcinoma: molecular pathways and therapeutic targets *Modern Pathology* 21(2), S37–S43.

Nikiforov, Y. E., Rowland, J. M., Bove, K. E., Monforte-Munoz, H. & Fagin, J. A. (1997). Distinct pattern of *ret* oncogene rearrangements in morphologic variants of radiation induced and sporadic thyroid papillary carcinomas in children. *Cancer Research* 57, 1690–1694.

Nikiforova, M. N. & Nikiforov, Y. E. (2009). Molecular diagnostics and predictors in thyroid cancer. *Thyroid* 19(12), 1351–1361.

Nikiforova, M. N., Lynch, R. A., Biddinger, P. W., Alexander, E. K., Dorn, G. W. 2nd, Tallini, G., Kroll, T. G. & Nikiforov, Y. E. (2003). RAS point mutations and PAX8-PPAR gamma rearrangement in thyroid tumors: evidence for distinct molecular pathways in thyroid follicular carcinoma. *Journal of Clinical Endocrinology and Metabolism* 88, 2318–2326.

Ozko-Wojciechowska, M., Pfeifer, A., Rusinek, D., Pawlaczek, A., Zebracka-Gala, J., Kowalska, M., Kowal, M., Swiernicki, M., Krajewska, J., Gawlik, E., Chmielik, E., Czarnicka, A., Szpak-Ulczok, S. & Jarzab, B. (2015). The prevalence of somatic RAS mutations in medullary thyroid cancer – a Polish population study. *Endokrynologia Polska* 66(2), 121–125.

Penna-Martinez, M., Epp, F., Kahles, H., Ramos-Lopez, E., Hinsch, N., Hansmann, M. M., Selkinski, I., Grünwald, F., Holzer, K., Bechstein, W. O., Zeuzem, S., Vorländer, C. and Badenhoop, K. (2014). FOXE1 association with differentiated thyroid cancer and its progression. *Thyroid* 24(5), 845–851.

Pita, J. M., Figueiredo, I. F., Moura, M. M., Leite, V. & Cavaco, B. M. (2014). Cell cycle deregulation and TP53 and RAS mutations are major events in poorly differentiated and undifferentiated thyroid carcinomas. *Journal of Clinical Endocrinology and Metabolism* 99(3), E947–E957.

Qian, K., Liu, K. J., Xu, F., Chen, X. Y., Chen, G. N., Yi, W. J., Zhou, E. X. & Tang, Z. H. (2012). X-ray repair cross-complementing group 1 (*XRCC1*) genetic polymorphisms and thyroid carcinoma risk: a meta-analysis. *Asian Pacific Journal of Cancer Prevention* 13(12), 6385–6390.

Robledo, M., Gil, L., Pollán, M., Cebrián, A., Ruiz, S., Azañedo, M., Benitez, J., Menárguez, J. & Rojas, J. M. (2003). Polymorphisms G691S/S904S of *RET* as genetic modifiers of MEN 2A. *Cancer Research* 63, 1814–1817.

Romei, C., Elisei, R., Pinchera, A., Ceccherini, I., Molinaro, E., Mancusi, F., Martino, E., Romeo, G. & Pacini, F. (1996). Somatic mutations of the *ret* protooncogene in sporadic medullary thyroid carcinomas are not restricted to exon 16 and are associated with tumor recurrence. *Journal of Clinical Endocrinology and Metabolism* 81, 1619–1622.

Ryu, R. A., Tae, K., Min, H. J., Jeong, J. H., Cho, S. H., Lee, S. H. & Ahn, Y. H. (2011). *XRCC1* polymorphisms and risk of papillary thyroid carcinoma in a Korean sample. *Journal of Korean Medical Science* 26, 991–995.
Genetics of thyroid cancer

Sahasrabudhe, R., Estrada, A., Lott, P., Martin, L., Polanco Echeverry, G., Velez, A., Neta, G., Takahasi, M., Saenko, V., Mitsutake, N., Jaeger, E., Duque, C. S., Rios, A., Bohorquez, M., Prieto, R., Criollo, A., Echeverry, M., Tomlinson, I., TCUKIN and CORGI Consortiums, Carmona, L. G. & JTCSM Consortium (2015). The 8q24 rs6983267 G variant is associated with increased thyroid cancer risk. Endocrine Related Cancer 22(5), 841–849.

Santos, L. S., Branco, S. C., Silva, S. N., Azevedo, A. P., Gil, O. M., Manita, I., Ferreira, T. C., Limbert, E., Ruff, J. & Gaspar, J. F. (2012). Polymorphisms in base excision repair genes and thyroid cancer risk. Oncology Reports 28, 1859–1868.

Santos, M., Azevedo, T., Martins, T., Rodrigues, F. J. & Lemos, M. C. (2014). Association of RET genetic polymorphisms and haplotypes with papillary thyroid carcinoma in the Portuguese population: a case-control study. PLoS One 9(10), e109822.

Soares, P., Fonseca, E., Wynford-Thomas, D. & Sobrinho-Simões, M. (1998). Sporadic ret-rearranged papillary carcinoma of the thyroid: a subset of slow growing, less aggressive thyroid neoplasms? Journal of Pathology 185, 71–78.

Takahashi, M., Saenko, V. A., Rogounovitch, T. I., Kawaguchi, T., Drozd, V. M., Takigawa-Imamura, H., Aklevich, N. M., Ratanarajay, C., Mitsutake, N., Takamura, N., Danilova, L. I., Lushchik, M. L., Demidchik, Y. E., Heath, S., Yamada, R., Lathrop, M., Matsuda, F. & Yamashita, S. (2010). The FOXE1 locus is a major genetic determinant for radiation-related thyroid carcinoma in Chernobyl. Human Molecular Genetics 19(12), 2516–2523.

Tallini, G., Santoro, M., Helie, M., Carlmagnino, F., Salvatore, G., Chiappetta, G., Carcangiu, M. L. & Fusco, A. (1998). RET/PTC oncogene activation defines a subset of papillary thyroid carcinomas lacking evidence of progression to poorly differentiated or undifferentiated tumor phenotypes. Clinical Cancer Research 4, 287–294.

Uchino, S., Noguchi, S., Yamashita, H., Sato, M., Adachi, M., Yamashita, H., Watanabe, S., Ohshima, A., Mitsuyama, S., Iwashita, T. & Takahashi, M. (1999). Somatic mutations in RET exons 12 and 15 in sporadic medullary thyroid carcinomas: different spectrum of mutations in sporadic type from hereditary type. Japanese Journal of Cancer Research 90, 1231–1237.

Vasko, V., Ferrand, M., di Cristofaro, J., Carayon, P., Henry, J. F. & De Micco, C. (2003). Specific pattern of RAS oncogene mutations in follicular thyroid tumors. Journal of Clinical Endocrinology and Metabolism 88(6), 2745–2752.

Vinagre, J., Almeida, A., Popolu, H., Batista, R., Lyra, J., Pinto, V., Coelho, R., Celestino, R., Prazeres, H., Lima, L., Melo, M., da Rocha, A. G., Preto, A., Castro, P., Castro, L., Pardal, F., Lopes, J. M., Santos, L. L., Reis, R. M., Cameselle-Teijeiro, J., Sobrinho-Simões, M., Lima, J., Máximo, V. & Soares, P. (2013). Frequency of TERT promoter mutations in human cancers. Nature Communications 4, 2185.

Vodicka, P., Stetina, R., Polakova, V., Tulupova, E., Nacecarati, A., Vodickova, L., Kumar, R., Hanova, M., Pardini, B., Slyska, J., Musak, L., De Palma, G., Soucek, P. & Hemminki, K. (2007). Association of DNA repair polymorphisms with DNA repair functional outcomes in healthy human subjects. Carcinogenesis 28 (3), 657–664.

Volante, M., Rapa, I., Gandhi, M., Bussolati, G., Giachino, D., Papotti, M. & Nikiforov, Y. E. (2009). RAS mutations are the predominant molecular alteration in poorly differentiated thyroid carcinomas and bear prognostic impact. Journal of Clinical Endocrinology and Metabolism 94 (12), 4735–4741.

Wan, P. T., Garnett, M. J., Roe, S. M., Lee, S., Niculescu-Duvaz, D., Good, V. M., Jones, C. M., Marshall, C. J., Springer, C. J., Barford, D. & Marais, R. (2004). Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 116, 855–867.

Wang, X., Zhang, K., Liu, X., Liu, B. & Wang, Z. (2015). Association between XRCC1 and XRCC3 gene polymorphisms and risk of thyroid cancer. International Journal of Clinical and Experimental Pathology 8(3), 3160–3167.

Wang, Y. L., Feng, S. H., Guo, S. C., Wei, J. L., Li, D. S., Wang, Y., Wang, X., Wang, Z. Y., Ma, Y. Y., Jin, L., Ji, Q. H. & Wang, J. C. (2013). Confirmation of papillary thyroid cancer susceptibility loci identified by genome-wide association studies of chromosomes 14q13, 9q22, 2q35 and 8p12 in a Chinese population. Journal of Medical Genetics 50, 689–695.

Weber, F. & Eng, C. (2005). Editorial: germline variants within RET: clinical utility or scientific playtoy? Journal of Clinical Endocrinology and Metabolism 90(11), 6334–6336.

Xing, M., Westra, W. H., Tufano, R. P., Cohen, Y., Rosenbaum, E., Rhoden, K. J., Carson, K. A., Vasko, V., Larin, A., Tallini, G., Tolaney, S., Holt, E. H., Hui, P., Umbricht, C. B., Basaria, S., Ewertz, M., Tufaro, A. P., Califano, J. A., Ringel, M. D., Zeiger, M. A., Sidransky, D. & Ladenson, P. W. (2005). BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. Journal of Clinical Endocrinology and Metabolism 90, 6733–6739.

Yan, L., Yanan, D., Donglan, S., Na, W., Rongmiao, Z. & Zhifeng, C. (2009). Polymorphisms of XRCC1 gene and risk of gastric cardiac adenocarcinoma. Diseases of the Esophagus 22, 396–401.

Yip, L., Nikiforova, M. N., Yoo, J. Y., McCoy, K. L., Sung, M. T., Armstrong, M. J., Nicholson, K. J., Ohtori, N. P., Coyne, C., Hodak, S. P., Ferris, R. L., LeBeau, S. O., Nikiforov, Y. E. & Carty, S. E. (2015). Tumor genotype determines phenotype and disease-related outcomes in thyroid cancer: a study of 1510 patients. Annals of Surgery 262(3), 519–525.

Zedenius, J., Larsson, C., Bergholm, U., Bovee, J., Svensson, A., Hallgren, B., Grimelius, L., Backdahl, M., Weber, G. & Wallin, G. (1995). Mutations of codon 918 in the RET proto-oncogene correlate to poor prognosis in sporadic medullary thyroid carcinomas. Journal of Clinical Endocrinology and Metabolism 80, 3088–3090.