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Whole-exome sequencing and bioinformatic analyses revealed differences in gene mutation profiles in papillary thyroid cancer patients with and without benign thyroid goitre background

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Abstract
Background: Papillary thyroid cancer (PTC) is the most common thyroid malignancy. Concurrent presence of cytomorphological benign thyroid goitre (BTG) and PTC lesion is often detected. Aberrant protein profiles were previously reported in patients with and without BTG cytomorphological background. This study aimed to evaluate gene mutation profiles to further understand the molecular mechanism underlying BTG, PTC without BTG background and PTC with BTG background. Methods: Patients were grouped according to the histopathological examination results: (i) BTG patients (n = 9), (ii) PTC patients without BTG background (PTCa, n = 8), and (iii) PTC patients with BTG background (PTCb, n = 5). Whole-exome sequencing (WES) was performed on genomic DNA extracted from thyroid tissue specimens. Nonsynonymous and splice-site variants with MAF of ≤ 1% in the 1000 Genomes Project were subjected to principal component analysis (PCA). PTC-specific SNVs were filtered against OncoKB and COSMIC while novel SNVs were screened through dbSNP and COSMIC databases. Functional impacts of the SNVs were predicted using PolyPhen-2 and SIFT. Protein-protein interaction (PPI) enrichment of the tumour-related genes was analysed using Metascape and MCODE algorithm. Results: PCA plots showed distinctive SNV profiles among the three groups. OncoKB and COSMIC database screening identified 36 tumour-related genes including BRCA2 and FANCD2 in all groups. BRAF and 19 additional genes were found only in PTCa and PTCb. "Pathways in cancer", "DNA repair" and "Fanconi anaemia pathway" were among the top networks shared by all groups. However, signalling pathways related to tyrosine kinases were the most significantly enriched in PTCa while "Jak-STAT signalling pathway" and "Notch signalling pathway" were the only significantly enriched in PTCb. Ten SNVs were PTC-specific of which two were novel; DCTN1 c.2786C>G (p.Ala929Gly) and TRRAP c.8735G>C (p.Ser2912Thr). Four out of the ten SNVs were unique to PTCa. Conclusion: Distinctive gene mutation patterns detected in this study corroborated the previous protein profile findings. We hypothesised that the PTCa and PTCb subtypes differed in the underlying molecular mechanisms involving tyrosine kinase, Jak-STAT and Notch signalling pathways. The potential applications of the SNVs in differentiating the benign from the PTC subtypes requires further validation in a larger sample size.

Author Keywords
benign thyroid goitre; papillary thyroid cancer; single nucleotide variants; thyroid tumourigenesis; whole-exome sequencing

Index Keywords
BRCA2 protein, Fanconi anemia group D2 protein, genomic DNA; algorithm, Article, bioinformatics, cell structure, clinical article, controlled study, COSMIC, cytology, data base, DNA extraction, DNA sequencing, fine needle aspiration biopsy, gene frequency, gene mutation, goiter, histopathology, human, human tissue, ligation mediated polymerase chain reaction, MCODE, Metascape, nonsynonymous substitution, Notch signaling, OncoKB, principal component analysis, protein protein interaction, single nucleotide polymorphism, subtotal thyroidectomy, thyroid gland tissue, thyroid papillary carcinoma, total thyroidectomy, tumor suppressor gene, whole exome sequencing

Tradenames
AllPrep DNA/RNA/Protein Mini, Qiagen, Germany; NanoDrop 2000c, Thermo, United States; Qubit 2.0, Thermo, United States

Manufacturers
Qiagen, Germany; Thermo, United States

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