1.0 INTRODUCTION

1.1 Background

Congenital hypothyroidism (CH) occurs in babies who are born without the ability to produce adequate amount of thyroid hormones. CH is reported to affect 1 in 3000 - 4000 life birth (Amar-Singh, 2010; Delange, 1979; Fisher et al., 1979). Most cases of CH (80 - 90 %) result from dysembryogenesis of the thyroid gland. The remaining 10 - 20 % of cases are due to thyroid dyshormonogenesis or defects in intermediary steps of thyroid hormone synthesis (Gruters, 1992). A number of studies have shown that thyroid dyshormonogenesis is associated with defects in gene encoding proteins that are involved in thyroid hormone synthesis such as dual oxidase 2 (DUOX2) (Varela et al., 2006), solute carrier family 5 or sodium iodide symporter (SLC5A/NIS) (Pohlenz & Refetoff, 1999), thyroglobulin (Tg) (Ieiri et al., 1991), thyroid peroxidase (TPO) (Deladoey et al., 2008), and thyroid stimulating hormone, beta (TSHB) (Deladoey et al., 2003).

Among the candidate genes, mutations in the TPO are amongst the most common causes of dyshormonogenetic CH (Mangklabruks et al., 1991). The single gene for TPO is located on chromosome 2p25 which spans at least 150 kb and contains 17 exons (Endo et al., 1995). The full-length 3152 bp mRNA transcript TPO1 (GenBank accession number NM_000547.5) encodes 933 amino acids which consists a large extracellular fragment, single short transmembrane segment and short cytoplasmic tail. TPO protein plays important roles in the biosynthesis of thyroid hormone (Kimura et al., 1987; Magnusson et al., 1987). It catalyses the iodination of Tg and is involved in
the coupling of some of the iodonucleosyl residues to generate active iodothyronines, T₃ and T₄ (Cetani et al., 1995; Gardas et al., 1997).

The TPO enzyme activity depends on two conditions: (1) a proper protein folding and membrane insertion and (2) an intact catalytic region (Ruf & Carayon, 2006). Therefore, mutations that occur in the catalytic region or cause the production of premature TPO protein could lead to a decrease in TPO activity which subsequently causes dyshormonogenetic CH and/or hypothyroid goitre. To date, more than 60 mutations in the TPO gene have been described. The majority of the mutations are localised in exons 8, 9 and 10 that encode the catalytic heme-binding domain of the protein. The reported mutations include frame shift, missense, alternative-splicing, nonsense mutations and total gene deletion (Coleman & Tsongalis, 2009; Ris-Stalpers & Bikker, 2010). TPO defects are commonly inherited in an autosomal recessive mode (Park & Chatterjee, 2005) but autosomal dominant inheritance had also been reported (Fugazzola et al., 2003).

Over the years, many cases of thyroid carcinoma associated with dyshormonogenetic goitre have been reported (Alzahrani et al., 2006; Camargo et al., 2001; Chertok Shacham et al., 2012; Cooper et al., 1981; Medeiros-Neto et al., 1998). However, the influence of the TPO mutation on malignant transformation has rarely been discussed and remains unclear. Since a recent study had reported that alterations of the TPO gene was found in patients with Hashimoto’s thyroiditis and papillary thyroid cancer (Liu et al., 2010), defects in TPO gene might not only cause thyroid dyshormonogenesis but possibly involve in other thyroid diseases like thyroid carcinoma and autoimmune thyroid diseases.
1.2 Objectives of the study

Hot-spot mutations in the TPO gene in a cohort of 17 unrelated patients with CH due to thyroid dyshormonogenesis had previously been screened (Kang, 2010). A c.1159G>A mutation in exon 8 was identified in a patient (CHP41). The cohort size of unrelated patients had since increased. Therefore, the aims of the study were;

I. To screen for the c.1159G>A mutation in CHP41’s family members and other unrelated patients with dyshormonogenetic CH.

II. To further characterise for other nucleotide alterations in the entire exons of the TPO gene in unrelated patients with thyroid dyshormonogenesis and their family members.

III. To predict and study the effect(s) of the alteration(s) on the TPO activity/function.