GENERAL INTRODUCTION

The thyroid gland is a butterfly-shaped endocrine gland that is located in the lower front of the neck and secretes thyroid hormones (T_3 and T_4). Thyroid hormone is essential to help each cell in each tissue and organ to work right. Thyroxine or T_4 is the major thyroid hormone. To exert its effects, tetraiodothyronine (T_4) is converted to triiodothyronine (T_3) by the removal of an iodine atom. The amount of T_4 produced by the thyroid gland is controlled by TSH. Hypothyroidism is characterized by less production of thyroid hormones. There are many disorders which are associated with hypothyroidism.

Thyroid Peroxidase (TPO) enzyme catalyzes two important reactions of thyroid hormone synthesis: the iodination of tyrosine residues in thyroglobulin and phenoxy-ester formation between pairs of iodinated tyrosines to generate thyroid hormones (Kopp, 2005). TPO is a membrane-bound glycoprotein (102 kDa), found as a dimer (Baker et al., 1994). Each monomer consists of 933 amino acid residues and contains a peroxidase domain, three additional extracellular domains, a transmembrane helix and a short C-terminal intracellular tail (Banga et al., 1990). The additional extracellular domains have been identified by protein sequence alignments to be an EGF-like (epidermal growth factor) domain, a CCP (complement control protein) domain and a 16 kDa N-terminal domain which shows amino acid sequence homology with N-terminal sequence of myeloperoxidase (MPO) (Johnson et al., 1989). The human TPO gene (GenBank Accession # NT_033000) is located on chromosome 2p25 and spans approximately 150 Kb, containing 17 exons (Kimura et al., 1989). Full-length human TPO mRNA (GenBank Accession # NM_000547) is about 3 kb (Kimura et al., 1987; Libert et al., 1987). Multiple transcript variants encoding distinct isoforms have been identified for this gene (Asakawa, 1994; Rivolta et al., 2003). Mutation of TPO gene is a common cause of defective thyroid hormone synthesis (Abramowicz et al., 1992).
Mutations in TPO gene (particularly non-synonymous cSNPs) can lead to severe defects in thyroid hormone production, due to total iodide organification defects (TIOD) or partial iodide organification defects (PIOD). TPO mutations are inherited as autosomal recessive traits (Rivolta et al., 2003). Iodination of salt is the most effective and sustainable long-term public health measure for the prevention and control of iodide organification defects (IDD). But the iodination programme will not be effective if the gene mutations are the cause of dyshormonogenesis. Therefore, it is important to screen the percentage of people having gene mutations and iodine deficiency among the clinically identified thyroid patients.

Screening and identification of mutations in the TPO gene of patients with evidence of TIOD and PIOD has been done by several groups in different countries of the world like Argentina (Rivolta et al., 2003), Netherlands (Bakker et al., 2000), Japan (Kotani et al., 2003), Portugal (Rodrigues et al., 2005), China (Wu et al., 2002). But no studies have been reported on TPO mutations for the development of hypothyroidism in the Indian population, although this medical condition afflicts a significant number of Indians [occurring in ~8% of the population (Bavadam, 2006)]. The present investigation is aimed to screen the mutations/polymorphisms in TPO gene and their effects on the function of TPO gene leading to hypothyroidism in the population of West Bengal to establish the genetic etiology of the disease.
AIMS AND OBJECTIVES

The present proposal aims to

- Investigate the familial history and clinical manifestations of the hypothyroid patients.

- Diagnose what proportion of Indian hypothyroid patients screened is due to mutation/polymorphism in the TPO gene.

- Investigate what types of TPO mutations/polymorphisms are prevalent in screened population.

- Investigate what are the effects of these mutations/polymorphisms on the function of TPO.

- Delineate genetic defects in the TPO gene and the spectrum of thyroid dysfunction.