

# Good example of genetic correlates and pathophysiology of hyperthyroidism: an ove...

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## **Genetic Correlates and Pathophysiology of Hyperthyroidism: An Overview of salient aspects**

### Introduction

Disturbances in thyroid haemostasis can occur at the level of the pituitary gland, the thyroid gland itself or in the periphery. By definition, hyperthyroidism refers to disorders in which the principal abnormality is the overproduction of thyroid hormones in the thyroid gland. This overproduction can have diverse determinants including auto-immunity, hereditary factors, familial predisposition, and perhaps, some other less understood factors. Regardless of etiology, the result is an increase in transcription in cellular proteins, causing an increase in the basal metabolic rate. The predominant cause of hyperthyroidism is Grave's disease. Other less common causes include Thyroiditis, Multi nodular goiter and single autonomous nodule.

### **Thyroid haemostatis**

The two major influences on thyroid hormone physiology include body's requirement of thyroid hormone and availability of its key substrate iodide. Iodide supply is monitored in part through its effects on the plasma level of thyroid hormones, but mainly in the thyroid itself, where it depresses various aspects of thyroid function and the thyrocyte sensitivity for TSH. The thyroid hormone (TH) synthesis involves active iodide uptake (by thyroid transmembrane sodium iodide symporter), its oxidation by the enzyme thyroid peroxidase and incorporation into the thyroglobulin (TG) molecule to form monoiodotyrosine and diiodotyrosine. Coupling of these precursors lead to formation of Thyroxine (T4) and triiodothyronine (T3). Since TH enters the

cell unbound, the concentration of free rather than total hormone reflects more accurately the activity level of TH-dependent processes. Consequently, any process that causes an increase in the peripheral circulation of unbound thyroid hormone can cause thyrotoxicosis.

In addition to the circulating hormone levels, the cellular level physiological effects of thyroid hormones are a direct function of the integrity of TH nuclear receptors. In normal individuals, thyroid hemostasis involves a complex interplay of stimulatory and inhibitory factors. The well understood mechanism principally involves regulation of TH levels by the hypothalamic supraoptic nuclei and the thyrotrophs of the anterior pituitary. The homeostatic effect of TSH is to stimulate all the steps in thyroid hormone synthesis and its release from thyroid gland.

### **Immunologically-mediated hyperthyroidism**

The hallmark of Grave's disease, the major immunologically mediated form of hyperthyroidism, is production of agonistic auto antibodies to the thyroid stimulating hormone receptor (TSHR-Ab). In addition to release of TH and TG, they also stimulate iodine uptake, protein synthesis, and thyroid gland growth.

### **Genetic correlates**

The basic defect in Grave's disease is an HLA-related organ specific defect in suppressor T-lymphocyte function. Although the cause is not clearly known, evidence suggests a combination of genetic and environmental factors.

There is a clinical overlap and association of Graves's disease with autoimmune Hashimoto's thyroiditis, and other autoimmune

diseases (pernicious anemia, myasthenia gravis, Addison's disease). The disease is five times more common in women. White and Hispanic populations in the United States have a higher prevalence of hyperthyroidism in comparison with black populations. In Caucasians, Grave's disease is associated with HLAB8, DR3 and DR2. Further, 50% of monozygotic twins have been found concordant for hyperthyroidism as opposed to 5% of discordant twins. More recent studies attribute up to 80% of thyroid auto-immune susceptibility to genetic factors. Other studies allude to a role of trigger factors that initiate a cascade of events in genetically predisposed individuals.

The combined effect is the activation of thyroid directed helper T-lymphocytes which in turn stimulate specific B-lymphocytes to produce TSH-R Ab. Antibodies against other thyroid antigens such as thyroid peroxidase and TGs are also present in Grave's disease.

Hemodynamic effects of thyroid hormones are caused by their direct action on heart and blood vessels. In the peripheral vascular system there is increased production of metabolic end products and relaxation of arterial smooth muscle fibres causing a fall in peripheral vascular resistance. This ends up playing a central role in all hemodynamic changes caused by thyroid hormones. The development of ophthalmopathy and dermopathy, however, is less well characterized. Both these processes are also understood to be immunologically mediated but further research is needed to delineate its pathogenesis.

## Conclusion

Many recent advances have furthered our understanding of the pathophysiological and genetical basis of hyperthyroidism. As a niche specialty, development of new genetic methods like linkage analysis and genome wide associations (GWAS) will greatly facilitate gene mapping studies - a potential tool to more precisely elucidate the genetic correlates of hyperthyroidism.

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