Molecular Mechanisms of Thyroid Gland Development
*Insights from Clinical Studies and from Mutant Mice*

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**INTRODUCTION: CONGENITAL HYPOTHYROIDISM, A KEY TO UNDERSTAND THYROID GLAND DEVELOPMENT**

As in many other fields of biomedical research, the careful description of congenital disorders affecting the development of the thyroid ("experiments of nature") is an absolute prerequisite and an invaluable tool for generating hypotheses about the molecular mechanisms involved at various stages of the differentiation, migration, and growth of the gland (1). Several genes involved not only in thyroid function, but also in the organogenesis of the gland have been identified in the past few years (reviewed in ref. 2).
Renewed interest in the molecular pathophysiology of congenital hypothyroidism (CH), a common disorder affecting about 1 in 4000 newborns, has led to the generation of several mouse knockouts and to the identification of a small number of single gene defects in humans (reviewed in ref. 3). Even though a better understanding of CH in molecular terms will probably have no impact on treatment, it will be important for genetic counseling in these families. Furthermore, it may shed light on other, more complex and less easily treatable, congenital malformations.

CH is a heterogeneous condition, which is usually classified on the basis of the level of the defect and of its transient or permanent nature. When the hypothyroidism results from a defect in the thyroid itself, it is called primary. On the other hand, secondary (pituitary defects) and tertiary (hypothalamic defects) are often grouped together under the designation “central hypothyroidism.” Transient causes of primary (transplacental transfer of antithyroid drugs or of thyroid-stimulating hormone [TSH]-receptor blocking antibodies, chronic iodine deficiency, and/or acute iodine overload) or of central congenital hypothyroidism (immaturity of the hypothalamo-pituitary control mechanisms) will not be considered further in this chapter. Because the vast majority of cases of permanent CH are of the primary type, the focus of this review will be on the development of the thyroid itself. However, new mechanisms of central hypothyroidism that have contributed to our understanding of the role of TSH in the development of the thyroid will also be briefly discussed.

The causes of permanent primary CH fall under two broad categories: the most frequent, accounting for ~80% of cases, is called thyroid dysgenesis (a category including defective thyroid migration, resulting in ectopic tissue, and complete absence of thyroid or athyreosis) and is in general considered sporadic with a female predominance. However, in a large series, we have recently shown (4) that the female predominance was only significant for ectopy: in athyreosis, as in dyshormonogenesis, a known autosomal recessive condition (see below), the proportion of girls is not significantly different from 0.5, suggesting that a proportion of athyroseis may have autosomal recessive mechanisms. Other recent studies have revealed evidence for genetic transmission in about 2% of cases of thyroid dysgenesis (5) (see below).

The second cause of permanent primary CH, thyroid dyshormonogenesis, results from a defect in any one of the genes involved in thyroid hormone formation (the sodium/iodide symporter or NIS; pendrin or PDS; thyroglobulin or Tg; the genes responsible for H2O2 generation, ThOX1 and ThOX2; and thyroperoxidase or TPO), follows an autosomal recessive pattern of inheritance. In the latter situation, the gland is of normal shape and is in the normal position. Because the normal feedback mechanisms are operative, TSH is elevated and goiter often ensues. Thyroid dyshormonogenesis will not be considered in this chapter and the reader is referred to the excellent chapter by Refetoff et al. (6).

There is some confusion in the nomenclature regarding thyroid dysgenesis; because the lateral lobes of the gland develop only if the medial anlage has reached its normal position, an ectopic thyroid is by definition “hypoplastic” (hence the hypothyroidism). However, as discussed below, the mechanisms leading to defective or aberrant migration of the anlage differ from those leading to hypoplasia of a normally located gland (7). Therefore, it is essential to specify whether a hypoplastic gland is ectopic or orthotopic. However, this is not always done and makes the interpretation of some studies difficult. A further challenge in this area is that the distinction between the presence of a small ectopic gland and complete absence of any thyroid tissue is difficult to make in humans;