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3

Genetics and management of congenital hypothyroidism

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Several evidences support a relevant genetic origin for Congenital Hypothyroidism (CH), however familial forms are uncommon. CH can be due to morphogenetic or functional defects and several genes have been originally associated either with thyroid dysgenesis or dyshormonogenesis, with a highly variable expressivity and a frequently incomplete penetrance of the genetic defects. The phenotype-driven genetic analyses rarely yielded positive results in more than 10% of cases, thus raising doubts on the genetic origin of CH. However, more recent unsupervised approaches with systematic Next Generation Sequencing (NGS) analysis revealed the existence of hypomorphic alleles of these candidate genes whose combination can explain a significant portion of CH cases. The co-segregation studies of the hypothyroid phenotype with multiple gene variants in pedigrees confirmed the potential oligogenic origin of CH, which finally represents a suitable explanation for the frequent sporadic occurrence of this disease.

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Introduction

Congenital hypothyroidism (CH) is the most common preventable cause of mental retardation and is associated with 12-fold increased risk of multiple neonatal malformations that may cause additional disease complications [1–3]. A tendency toward an increased CH detection has been described in several socio-economically advanced countries [2–4]. Several concomitant factors (eg, improved outcome of CH more frequently allowing transmission of heritable defects, endocrine disrupting chemicals) can contribute this phenomenon, but the lower threshold of neonatal TSH screening represents the main cause of the increased CH detection [5]. CH is a highly heterogeneous disease characterized by a wide spectrum of thyroid function impairment and a variable origin, as both functional and developmental defects can account for its pathogenesis [6–8]. The percentages of cases with thyroid dysgenesis (athyreosis, ectopy, hemiagenesis or hypoplasia) or functional defects with a thyroid-in-situ are similar in recent CH series [2,3,9].

CH is typically reported to be sporadic but several findings in humans and experimental models support a relevant genetic origin. Until recently, CH was considered as a puzzle of monogenic diseases and the investigations on its pathogenesis were oriented by phenotype [6–8,10–13]. By using such strategy, pathogenic variations in candidate genes have been found in <10% of the cases [6–8], but genetic studies targeting specific phenotypes or particular ethnic groups yielded higher mutation detection rates [14–17]. On these bases, CH has been considered as a disease with a strong genetic component, but with a largely missing explanation for its heritability.

The advent of next generation sequencing (NGS) allowing the simultaneous and systematic analysis of known candidate genes (targeted NGS) or of the entire exome or genome (whole exome or genome sequencing, WES or WGS, respectively) [18,19] recently opened novel perspectives on the pathogenesis of CH, that are consistent with: a) previous findings obtained in animal models, b) epidemiological data, and c) the variable expression and penetrance of genetic defects within familial settings.

Known candidate genes for CH pathogenesis and related phenotype presentation

Numerous genes are known to be required for thyroid hormone synthesis. The evidence supporting the role of these genes has been generally obtained in animal models, by co-segregation studies in humans or by functional studies of the identified loss-of-function (LOF) variants. The Tables 1 and 2 summarize the candidate genes, respectively, for the morphogenetic or functional defects, together with the associated phenotype manifestations in the classic monogenic forms.

The disorders of thyroid morphogenesis

The defects of thyroid morphogenesis are classified as athyreosis (lack of thyroid tissue), ectopy, hemiagenesis (hypoplasia of one thyroid lobe) or hypoplasia (Table 1). These defects are generally reported as sporadic, but the discovery of candidate genes argues in favor of a heritable origin of thyroid dysgenesis, and uncovered the highly variable degree of expressivity and penetrance of inherited variants in the affected families. Accordingly, the French CH network reported frequent thyroid developmental abnormalities in relatives of patients with thyroid dysgenesis [20].

NKX2-1, also known as TTF1 (thyroid transcription factor-1), is a homeodomain (HD)-containing protein belonging to the NKX2 family of transcription factors. In mice, *Nkx2-1* transcripts and the corresponding encoded protein were identified in the thyroid anlage since the time of its specification, as well as during adulthood. *Nkx2-1* is essential for the survival of the thyroid precursors, for folliculogenesis, and for supporting the expression of thyroid-specific genes such as *Tg, Tpo*, *Tshr,* and *Slc5a5* (*Nis*) [6,7,21]. Expression of *Nkx2-1* was also detected in the endodermal cells of the lung bud and in the bronchial epithelium. In the lung, Nkx2-1 regulates the expression of SP (surfactant protein)-A, SP-B, SP-C, and other lung-specific genes. In the central nervous system (CNS), the expression of *Nkx2-1* is observed in restricted regions of the ventral forebrain including the hypothalamus [6,7,21]. In humans, starting from developmental days 32 and 33, transcripts of *NKX2-1* are

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