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Advances and Perspectives in Genetics of Congenital Thyroid Disorders

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Introduction

Congenital hypothyroidism (CH) is the most frequent endocrine disease in infants, affects about 1 in 3,000 newborns and is characterized by elevated levels of thyroid-stimulating hormone (TSH) as a consequence of reduced thyroid function. It is also one of the most common preventable causes of cognitive and motor deficits. Prevention of CH is based on carrier identification, genetic counseling and prenatal diagnosis. In neonates a complete diagnosis of CH should include clinical examination, biochemical thyroid tests, thyroid ultrasound, radioiodine or technetium scintigraphy and perchlorate discharge test (PDT). In the last two decades, considerable progress has been made in identifying the genetic and molecular causes of CH. Knowing the prevalence of mutations in each population will facilitate greatly the molecular genetic testing. The classification based on the genetic alterations divides CH into two main categories caused: (a) by disorders of thyroid gland development (dysembriogenesis or thyroid dysgenesis group) or (b) by defects in any of the steps of thyroid hormone synthesis (dyshormonogenesis group) [1]. The dysembryogenesis or thyroid dysgenesis group, which accounts for the 80-85% of the cases, results from a thyroid gland that is completely absent in orthotopic or ectopic location (agenesis or athyreosis), severely reduced in size but in the proper position in the neck (orthotopic hypoplasia) or located in an unusual position (thyroid ectopy) at the base of the tongue or along the thyroglossal tract [1]. In only 5% of the patients, the CH is associated with mutations in genes responsible for the development or growth of thyroid cells: *NKX2.1* (also known as *TTF1* or *T/EBP*), *FOXE1* (also known as *TTF2* or *FKHL15*), paired box transcription factor 8 (*PAX-8*), *NKX2.5*, and *TSHR* genes [1]. Consequently, the genetic mechanisms underlying the defects in thyroid organogenesis in the majority of the cases remain to be elucidated. Epigenetic mechanisms leading to stochastic variations in the expression of multiple loci could be responsible for the sporadic characteristic of thyroid dysgenesis.

Dyshormonogenesis, which accounts for the remaining 15-20% of the cases, has been linked to mutations in the *SLC5A* (Na+/I_ symporter, *NIS*) [2], *SLC26A4* (Pendrine, *PDS*) [3], thyroperoxidase (*TPO*) [4], dual oxidase2 (*DUOX2*), *DUOX* maturation factor 1 and 2 (*DUOXA1* and *DUOXA2*) [5-7], iodotyrosine dehalogenase 1 (*DEHAL1*) [8] and thyroglobulin (*TG*) [1] 27 genes. These mutations produce a heterogeneous spectrum of congenital hypothyroidism, with an autosomal recessive inheritance. Thereafter, the patients are typically homozygous or compound heterozygous for the gene mutations and the parents, carriers of one mutation.

Human *TG* gene is a single copy gene of 270 kb long that maps on chromosome 8q24.2- 8q24.3 and contains an 8.5 kb coding sequence divided into 48 exons [1]. A leader peptide of 19 amino acids is followed by a polypeptide of 2,748 amino acids. *TG* represents a highly specialized homodimeric glycoprotein for thyroid hormone biosynthesis. Mutations in the *TG* gene lead to permanent congenital hypothyroidism. The presence of low *TG* level and also negative perchlorate discharge test (*PDT)* in a goitrous individual suggests a TG gene defect [1]. Patients with iodotyrosine dehalogenase deficiency will also develop goiter with hypothyroidism, when dietary iodide is limiting. In these patients the perchlorate discharge test does not show increased release of radioiodine after administration of the competitor, indicating that the organification process itself is not affected, whereas the serum TG levels are elevated [8]. Patients with an iodide transport defect by mutations in SLC5A gene have a normal-sized or somewhat enlarged thyroid gland, elevated plasma TG levels and no radio-iodide uptake [2].

Iodide organification defects are associated with mutations in the *TPO*, *DUOX2*, *DUOXA2* or *SLC26A4* genes and characterized by a positive *PDT* [1]. Mutations in *SLC26A4* gene cause Pendred syndrome characterized by congenital sensorineural hearing loss and goiter without or with hypothyroidism [3]. *TPO* is a membrane-bound glycoprotein located at the apical membrane of the thyroid follicular cells that catalyses iodide oxidation and organification in the *TG* tyrosine residues, leading to the thyroid hormone synthesis (T3 and T4) by coupling of iodotyrosine residues. The *TPO* gene

is located on the short arm of chromosome 2 (2p25). It comprises 17 exons, covers approximately 150 kb of genomic DNA and codes 933 amino acids [4]. The mRNA is 3,048 nucleotides long and the pre-protein is composed of a putative 14 amino acids signal peptide followed by a 919 amino acids polypeptide which codifies a large extracellular domain, a transmembrane domain, and a short intracellular tail. H2O2 is used as a substrate by *TPO* in the organification of iodide. The H2O2 generation system of the thyroid involves a metabolic pathway which includes the complex *DUOX1*/*DUOX2*//*DUOXA1*/*DUOXA2* [5-7]. The *DUOX1* and *DUOX2* genes encoding similar proteins that are inserted in the apical membrane of thyroid cells. These proteins are known as dual oxidase because they have both a peroxidase homology ectodomain (peroxidase-like domain) and a g*p91phox*/*NOX2*-like domain [5-7]. The *DUOX2* gene is located on chromosome 15q15.3 spanning 22 Kb of genomic DNA which includes 34 exons, being the first one non-coding. The mRNA is 6,376 nucleotides long and the preprotein is composed of a putative 25 amino acids signal peptide followed by a 1,523 amino acids polypeptide [5-7]. *DUOX1* gene encodes a homologous protein displaying 83 % sequence similarity [5-7]. The 36 kb *DUOX1* gene consists of 35 exons (being the first two noncoding) encoding a protein of 1551 amino acids which first 21 amino acids correspond to the signal peptide. *DUOXA1* and *DUOXA2* are endoplasmatic reticulum (ER)-resident proteins, essential for *DUOX* maturation. The *DUOXA* and *DUOXA2* genes are oriented head to head in the intergenic region of 16 kb between both *DUOX* genes [7].

Recent technological advances in instrumentation, computer hardware and software for next-generation sequencing (NGS) platforms have led to the identification of new mutations in the *DUOX2*, *TPO* and *TG* genes, [9-15]. *DUOX2* gene mutations are considered a common cause of dyshormonogenesis which prevalence is high in Asian population [9-14]. Both biallelic and monoallelic DUOX2 mutations led to a clinical spectrum ranges from subclinical hypothyroidism to transient or permanent congenital hypothyroidism. To date, 118 deleterious mutations in the human *DUOX2* gene have been identified and characterized: 6 splice site mutations, 11 nonsense mutations, 76 missense mutations and 25 deletions or insertions [5,6,9-14]. Interestingly, Fu et al. [11,12] using NGS platform detected that most of the cases of CH with one or two *DUOX2* mutations are associated to subclinical or transient congenital hypothyroidism, whereas patients with three or four (one in homozygous) or five (two in homozygous) *DUOX2* mutations are mostly associated with permanent CH. The new technologies allow also the identification in the same patient with CH the coexistance of multiple mutations in different thyroid genes; for instances mutations in *DUOX2* associated with mutations in *DUOXA2* or *TPO* or *TG* or *TSHR* or *SLC26A4* [9,11,12,14].

In conclusion, here we discussed remarkable advances in the understanding of the pathophysiology the CH as well as in the identification of the mutations responsible for the disease. However, the impact of several points on the development of the CH remains to be elucidated. The introduction of NGS approaches, characterized by a marked increase in the yield of DNA sequencing and the ability to analyze large populations will probably allow a change in the traditional understanding of the molecular and genetic bases of CH and the genotype phenotype correlation. The identification of the coexistence of multiple mutations in the same gene or in different thyroid specific genes could contribute to the accurate diagnosis and classification of the defects. Moreover, the massive identification of mutations could be greatly important in the near future, since preimplantation genetic diagnosis will be available for families in which the genetic defects responsible for the CH have been identified.

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