 Advances and Perspectives in Genetics of Congenital Thyroid Disorders

Héctor M Targovnik, Cintia E Citterio, Sofi Siff and Carina M Rivolta

University of Buenos Aires, National Research Council and (CONICET ), Institute of Immunology , Genetics and Metabolism ( INIGEM ), Faculty of Pharmacy and Biochemistry, Hospital de Clínicas "José de San Martín", Buenos Aires, Argentina

Corresponding author: Targovnik HM, University of Buenos Aires, National Research Council and (CONICET), Institute of Immunology, Genetics and Metabolism (INIGEM), School of Pharmacy and Biochemistry, Hospital de Clínicas "José de San Martín", Av. Córdoba 2351, Fourth Floor, Room 5, C1120AAP - Buenos Aires, Argentina, Tel: +54-11-5950-8805; E-mail: htargovn@ffyb.uba.ar

Received date: Sept 02, 2016, Accepted date: Sept 21, 2016, Published date: Sept 23, 2016

Copyright: © 2016 Targovnik HM, et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.


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, radiiodine 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 major 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 athyrrosis), 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: NKKX2.1 (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], thyroxoperoxidase (TPO) [4], dual oxidase2 (DUOX2), DUOX maturation factor 1 and 2 (DUOX1 and DUOX2) [5-7], iodotyrosine dehalogenas 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 mature peptide 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 organisation 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 organization 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 gp91phox/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 DUOX 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 monallelic 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 coexistence 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.

Acknowledgements

H.M. Targovnik and C.M. Rivolta are established investigators of the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET). S. Siffo is research fellows of the Fondo para la Investigación Científica y Tecnológica (FONCyT- ANPCyT-MINCyT). C.E. Citterio is a posdoctoral research fellow of CONICET. This study was supported by grants from the FONCyT-ANPCyT-MINCyT (PICT 2014-1193 to CMR, PICT 2012-1090 and PICT 2015-1811 to HMT), CONICET (PIP 2015-11220150100499 to CMR) and Universidad de Buenos Aires (UBACyT 2016-2002015010099BA to CMR).

References


