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Editorial note:

Congenital hypothyroidism is the most common endocrine disease in infants. Through early identification and treatment of affected patients, delays in cognitive and motor development can be effectively prevented. In this topical update, Dr Liz Yuen reviews the aetiology and shares recent advances in understanding the molecular basis of congenital hypothyroidism. Genetic diagnosis and counselling can be provided to affected families regarding prognosis and recurrence risk. We welcome any feedback or suggestions. Please direct them to Dr. Poon Wing Tat (e-mail: poonwt@ha.org.hk) of Education Committee, the Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.

Thyroid Dyshormonogenesis

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Abbreviations

CH	Congenital hypothyroidism
PIOD	Partial iodide organification defect
T3	3,5,3'-Tri-iodothyronine
T4	3,5,3',5'-Tetra-iodothyronine or thyroxine
TG	Thyroglobulin
TIOD	Total iodide organification defect
TPO	Thyroid peroxidase
TSH	Thyroid stimulating hormone

Introduction

Congenital hypothyroidism (CH) is an important preventable cause of mental retardation. To prevent irreversible brain damages caused by hypothyroidism, sufficient doses of thyroxine should be started within a few weeks after birth.(1) Since neonates with CH have no obvious or minimal clinical manifestations, biochemical screening in the newborn period has become the best public health strategy for early detection of affected neonates. In Hong Kong, a territory-wide screening programme for CH was started in 1984.(2) Cord blood samples are collected immediately after birth for measurement of thyroid stimulating hormone (TSH) by a single laboratory dedicated for newborn screening. The incidence of CH in Hong Kong was reported to be 1 in 2,404, which is comparable to that in other populations.(2-6)

Causes of congenital hypothyroidism

The aetiologies of CH are summarized in Table 1.(7) Approximately 80 - 85% of CH are caused by thyroid dysgenesis, which is a group of congenital disorders of thyroid gland development or migration. Affected patients may have complete thyroid gland aplasia, hypoplasia or ectopic glands. The large majority of thyroid dysgenesis cases are sporadic and only about 5% has a genetic basis.(8,9) Thyroid dyshormonogenesis describes a group of inherited disorders which affect the biochemical pathway of thyroid hormone synthesis. These disorders collectively account for 10 - 15% of CH cases. Approximately 1/4 of patients with CH in Hong Kong have some forms of thyroid dyshormonogenesis.(10) Some neonates detected by newborn screening program have transient instead of permanent CH. Although this subgroup of patients does not require life-long thyroid hormone replacement, early identification and treatment in early years of life is equally important.(11) The time course of recovery of the hypothalamic-pituitary-thyroid axis in patients with transient CH depends on the underlying cause. Although most of the transient CH are due to acquired conditions such as iodine deficiency or maternal transfer of autoantibodies, a few genetic causes have been described.(11,12)

Table 1 Aetiology of congenital hypothyroidism (modified from reference 7)

Primary congenital hypothyroidism
▸ Thyroid dysgenesis (ectopic, aplasia, hypoplasia)
▸ Thyroid dyshormonogenesis
▸ Resistance to TSH binding or signaling
Secondary congenital hypothyroidism
▸ Isolated TSH deficiency
▸ Congenital hypopituitarism
Peripheral congenital hypothyroidism
▸ Thyroid hormone transport defect
▸ Thyroid hormone metabolism defect
▸ Thyroid hormone resistance
Transient congenital hypothyroidism
▸ Prematurity
▸ Maternal or neonatal excess iodine exposure
▸ Maternal or neonatal iodine deficiency
▸ Maternal antithyroid drugs
▸ Maternal TSH-receptor blocking antibodies (TRB-Ab)
▸ Thyroid dyshormonogenesis caused by *DUOX2* or *DUOXA2* mutations
▸ Congenital hepatic haemangiomas
▸ Protein-losing nephrosis

Biochemistry of thyroid hormone synthesis and their defects

The basic components required for thyroid hormone synthesis are specific tyrosyl residues on thyroglobulin (TG, encoded by the *TG* gene) and iodine. Iodide ions in the circulation are taken up by the thyroid gland via the sodium-iodide symporter (NIS, encoded by the *SLC5A5* gene) located at the basolateral membrane of the thyroid follicular cells. The iodide ions are then concentrated in the colloid by passing through the pendrin protein (encoded by the *SLC26A4* gene) on the apical side of the follicular cell membrane. Inside the follicular lumen (i.e. colloid), iodide ions are first oxidized to iodine radicals and then incorporated to tyrosyl residues on TG to form monoiodotyrosine (MIT) or di-iodotyrosine (DIT).

Coupling of one MIT and one DIT or two DITs forms the final active thyroid hormones 3,5,3'-tri-iodothyronine (T3) and 3,5,3',5'-tetra-iodothyronine (T4), respectively. The iodide organification and iodotyrosine coupling steps are catalyzed by the enzyme thyroid peroxidase (TPO, encoded by the *TPO* gene) in the presence of hydrogen peroxide which acts as the ultimate electron acceptor. The thyroid hydrogen peroxide-generating system is composed of two dual oxidase enzymes DUOX1 and DUOX2 (encoded by the *DUOX1* and *DUOX2* genes, respectively) and their corresponding maturation factors DUOXA1 and DUOXA2 (encoded by the *DUOXA1* and *DUOXA2* genes, respectively). DUOX2 is preferentially expressed in human thyroid tissue.(13) Subsequent evidence demonstrated that DUOX2/DUOXA2 is the predominant enzyme system in the thyroid while the exact role of DUOX1/DUOXA1 in the thyroid remains unknown.(11) Under TSH stimulation, TG is endocytosed into the follicular cells and metabolized by lysosomal enzymes. This process releases T4 and T3, which diffuse through cellular membrane and enter the thyroidal circulation. Iodide ions bound to DIT and MIT are recycled by the enzyme iodotyrosine deiodinase (encoded by the *IYD* gene) for further thyroid hormone synthesis.

Defects in any component of the above described thyroid hormone synthetic pathway can cause thyroid dyshormonogenesis (Table 2).(14) Except the case of NIS defect caused by *SLC5A5* mutations, patients with thyroid dys-hormonogenesis are characterized by a large orthotopic thyroid gland with increased radionuclide uptake.(7) Perchlorate discharge test, which involves the administration of radioactive iodine followed by perchlorate and serial monitoring of radioactivity of the thyroid gland, is the conventional method used to sub-classify patients with thyroid dyshormonogenesis. In normal subjects, less than 10% of the radioactive iodine is discharged after the administration of perchlorate. Patients with *TPO* mutations are characterized by a rapid and almost complete release of radioactive iodide in perchlorate discharge test (i.e. total iodide organification defect, TIOD). Both TIOD and partial iodide organification defect (PIOD) have been described in patients with *DUOX2* mutations.(11) Defects in *SLC26A4* (Pendred syndrome) and *DUOXA2* are associated with PIOD.(11)

In the following parts, more details about the 5 nonsyndromic forms of thyroid dyshormonogenesis will be described, i.e. sodium-iodide symporter defect caused by *SLC5A5* mutations, thyroglobulin deficiency caused by *TG* mutations, thyroid peroxidase deficiency caused by *TPO* mutations, hydrogen peroxide-generation defect caused by *DUOX2* or *DUOXA2* mutations and iodotyrosine deiodinase deficiency caused by *IYD* mutations. Readers may refer to the recent reviews by Choi *et al*. and Bizhanova and Kopp for details about the molecular basis of Pendred syndrome and its association with hypothyroidism.(15,16)

Sodium-iodide symporter

The first case of CH caused by a homozygous mutation in the *SLC5A5* gene, which encodes the sodium iodide symporter (NIS), was described in 1997.(17) Patients with NIS defect are characterized by a normal orthotopic thyroid gland with no to minimal radionuclide uptake. Therefore, if ultrasonography is not routinely performed, these patients can be easily misdiagnosed to have thyroid aplasia. The phenotypes of NIS defects are broad with some patients present at birth while others present during childhood or even in adulthood.(18,19) Therefore, patients with NIS defects may not be detected by newborn screening. Iodine supply is a known factor which influences the clinical manifestations of patients with NIS defects. Iodide supplement is as effective as thyroxine replacement in treating these patients.(19)

Thyroid peroxidase deficiency

Thyroid peroxidase (TPO) is the enzyme which catalyses the iodination of tyrosyl residues on TG and the coupling of iodotyrosines to form thyroid hormones. *TPO* mutations account for approximately 40% of thyroid dyshormonogenesis in various populations.(20-22) Previous studies in Taiwanese patients showed that TPO defect was

the most common form of thyroid dyshormonogenesis and many patients were either homozygous or heterozygous for the insertion mutation c.2268dupT.(22,23) Haplotype analysis in eight patients who were homozygous for c.2268dupT strongly suggested that it was a founder mutation in Taiwan.(22) In addition, heterozygosity for c.2268dupT have been demonstrated to be an important susceptibility factor in Taiwanese patients with transient CH.(24)

Thyroglobulin deficiency

Thyroglobulin (TG) is the most abundant protein in the matrix of thyroid follicles. It provides tyrosyl residues for synthesis of thyroid hormones and serves as a reservoir of thyroid hormones. Therefore, mutations in the *TG* gene that result in defective synthesis or metabolism of TG can lead to CH.(25,26) Previous studies in Taiwanese patients showed that TG defects accounted for 38% of thyroid dyshormonogenesis.(22,27) Patients with TG defects have a orthotopic thyroid gland with normal to raised radionuclide update and very low serum TG concentrations. To obtain meaningful result, sample for TG measurement should be collected before commencement of thyroxine replacement.

Defects in the generation of hydrogen peroxide
DUOX2

Mutation in *DUOX2* is now a well-known cause of CH.(11,28) However, the exact genotype-phenotype correlation, especially the relation between the severity of hypothyroidism and number of *DUOX2* mutations, remains unresolved. The first report that described *DUOX2* mutations in patients with CH were published in 2002 by a group from the Netherlands.(28) Among 45 patients with permanent CH and TIOD, one was found to harbour homozygous *DUOX2* mutations. In addition, in 3 out of 8 patients with transient CH and PIOD, heterozygous *DUOX2* mutations were identified. All four *DUOX2* mutations described in this study were predicted to create premature stop codons and abolish the hydrogen peroxide-generating domain of the DUOX2 enzyme. This group of investigators for the first time demonstrate a genetic basis for transient CH and postulates that affected patients only develop biochemical and clinical abnormalities at periods of high thyroxine requirement e.g. early infancy, puberty and pregnancy. Therefore, they suggest that long-term follow-up of patients with monoallelic *DUOX2* mutations may be necessary as these patients are prone to develop recurrent hypothyroidism later in life.(28)

Subsequent studies showed that the inheritance patterns of *DUOX2* mutations is more complex than that proposed by previous studies.(11,29,30) In 2008, Maruo and co-workers described biallelic *DUOX2* mutations in eight Japanese patients (2 familial and 2 sporadic) with transient CH.(Maruo 2008) In particular, a family with 4 affected siblings affected by transient CH were found to be compound heterozygous for 2 *DUOX2* frameshift mutations (p.L479SfsX2 and p.K628RfsX10). Both mutations were predicted to result in total loss of DUOX2 activity. Some degree of intra-familial phenotypic variation was also observed in this family. The youngest affected sibling had elevated TSH but normal free T4 at initial evaluation. His TSH gradually returned to normal at 2 months of age without any thyroxine supplementation. Furthermore, the only unaffected sibling with heterozygous p.L479SfsX2 mutation had normal TSH in newborn screening and did not develop transient CH.

Based on the reported cases with *DUOX2* mutations, it is obvious that the genotype-phenotype correlation is not straightforward. Patients with biallelic *DUOX2* mutations may develop either permanent or transient CH, while patients with monoallelic *DUOX2* mutations may or may not develop hypothyroidism in the neonatal period. The natural course and severity of hypothyroidism not only depends on the number *DUOX2* mutations present in the genome, other genetic (e.g. *DUOX1*) and environmental factors (e.g. supply of iodine) may also play a role.(11,31)

DUOXA2

Dual oxidase maturation factor 2 (DUOXA2) plays a crucial role in the maturation and

translocation of DUOX2 from the endoplasmic reticulum to the plasma membrane.(32) *DUOXA2* was first described as a cause of CH in 2008.(33) In this study, 10 Caucasian patients and one Chinese patient with CH and PIOD were recruited. Interestingly, only in the Chinese patient but not the Caucasian patients, a homozygous nonsense *DUOXA2* mutation p.Tyr246* was detected. Follow-up study of this Chinese patient at 7 years of age, one month after cessation of thyroxine replacement, showed a slight elevation of TSH (5.0 mU/L, reference range 0.4 – 4.0) and normal free T4. Further studies detected one heterozygous carrier of p.Tyr246* among 92 Chinese controls, and none in 89 Caucasians and 41 Japanese controls.(33) Results of this study demonstrated that biallelic *DUOXA*2 mutations is a cause of mild CH. They also suggested that p.Tyr246* in the *DUOXA2* gene was a common mutation among the Chinese population. A recent study from the Mainland China found one out of 47 CH patients with compound heterozygous *DUOXA2* mutations, and one of the detected mutation was p.Tyr246*.(34) This result provides further evidence that *DUOXA2* mutations, p.Tyr246* in particular, is relatively common among the Chinese population.

Iodotyrosine deiodinase deficiency

Iodotyrosine deiodinase is the enzyme responsible for recycling of intra-thyroidal iodide from MIT and DIT. The clinical severity of iodotyrosine deiodinase deficiency is highly heterogeneous, but in contrast to other thyroid dyshormonogenesis, affected patients are typically missed by newborn screening.(35) Therefore, a significant proportion of affected patients were identified late and thus developed mental and growth retardation. Iodotyrosine deiodinase is encoded by the *IYD* gene and the first report of *IYD* mutations in hypothyroid patients was published in 2008.(36) Although most reported cases appear to inherit the disease in an autosomal recessive manner, patients carrying heterozygous *IYD* mutations, who developed goiter and hypothyroidism, have also been described.(37) Therefore, it is speculated that the phenotypes of iodotyrosine deiodinase deficiency are influenced by environmental factors (e.g. iodine supply) and possibly other genetic factors. The biochemical hallmark of iodotyrosine deiodinase deficiency is an excessive excretion of MIT and DIT in urine. In some instances, this may be the only clue to diagnosis.(38) However, this biochemical test is not readily available in local laboratories.

Conclusion

Congenital hypothyroidism is the most common endocrine disease in infants. Like other developed countries, Hong Kong has a well-structured newborn screening programme in place with over 99% coverage.(2) Through early identification and treatment of affected patients, delays in cognitive and motor development can be effectively prevented. However, little clinical attention is paid to the aetiology of CH despite all the recent advances in molecular biology. In most paediatric centers, other than confirmatory serum TSH and free T4 concentrations, only minimal additional investigation (e.g. thyroid radionuclide scan) is done to delineate the underlying cause of CH.

Recent advances in molecular biology have greatly improved our knowledge and understanding on each individual form of thyroid dyshormonogenesis. With a genetic diagnosis, precise counselling can be provided to affected families regarding prognosis and recurrence risk.(39) In particular, female patients with *DUOX2* mutations may be at risk of recurrent hypothyroidism during pregnancy, which requires thyroxine replacement to prevent adverse neurodevelopmental outcome in the fetus. In addition, some forms of thyroid dys-hormonogenesis such as NIS defect and iodotyrosine deiodinase deficiency may be beneficial to iodide supplementation. Furthermore, a genetic diagnosis facilitates the identification of asymptomatic family members who are at risk of developing hypothyroidism later in life.

Addition of thyroid ultrasonography and measurement of TG into the local routine evaluation protocol of neonates with abnormal newborn screening results helps stratify them for appropriate genetic testing. Previous studies have shown that several hot spot mutations are present

in the Chinese population, e.g. c.2268dupT in the *TPO* gene and p.Tyr246* in the *DUOXA2* gene. Further studies are required to confirm whether the local Chinese patients with CH share a similar genetic basis.

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Table 2. Genes associated with thyroid dyshormonogenesis

Gene	Protein product	Chromosomal locus	Defects	Perchlorate discharge test
SLC5A5	Sodium-iodide symporter	19p13.11	Iodide trapping defect	Normal
SLC26A4	Pendrin	7q22.3	Defect in apical iodide efflux / Pendred syndrome	PIOD
TG	Thyroglobulin	8q24.22	Defect in synthesis of thyroglobulin	PIOD
TPO	Thyroid peroxidase	2p25.3	Defect in thyroid peroxidase activity	TIOD
DUOX2	Dual oxidase 2	15q21.1	Defect in hydrogen peroxide generation	PIOD or TIOD
DUOXA2	Dual oxidase maturation factor 2	15q21.1	Defect in hydrogen peroxide generation	PIOD
IYD	Iodotyrosine deiodinase	6q25.1	Defect in recycling of intrathyroidal iodide	Normal