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Variants in the Thyroglobulin Gene in Patients with Iodide Transport Defect

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Introduction

Congenital hypothyroidism, the most common inborn disorder detected in newborn screening programmes, is a prenatal hypothalamic-pituitary-thyroid axis dysfunction that results in thyroid hormone deficiency. Although iodine deficiency is still the most common cause of hypothyroidism at birth, in iodide-sufficient areas, more than 65% of these patients have abnormalities in thyroid organogenesis (dysgenesis), with the remaining 35% developing eutopic thyroid glands with impaired thyroid hormonogenesis (dyshormonogenesis). Recent European Reference Network on Rare Endocrine Conditions consensus guidelines recommend molecular diagnosis using next-generation sequencing [1-3] to investigate the genetic basis of the disease, as well as facilitating interdisciplinary patient follow-up and ensuring adequate genetic counselling to families.

Current consensus guidelines also recommend that after the disease is identified in neonatal screening, the biochemical confirmatory diagnosis be followed by complementary biochemical and imaging studies to gain a better understanding of the disease's underlying aetiology, particularly by using Sanger sequencing-based approaches to evaluate the sequence of candidate genes. A variable degree of hypothyroidism, reduced to absent radioiodide accumulation in a normal to hyperplastic eutopic thyroid gland, a low saliva-to-plasma iodide ratio, and normal to increased thyroglobulin (TG) serum levels are all symptoms of congenital iodide transport defect, an autosomal recessive disorder caused by impaired iodide accumulation in the thyroid follicular cell.

Description

Iodide accumulation in the thyroid follicular cell is a critical requirement for thyroid hormonogenesis because iodine is a critical component of thyroid hormones. The sodium/iodide symporter (NIS) is a basolateral plasma membrane glycoprotein that is involved in iodide accumulation in thyroid follicular cells. This protein's carboxy-terminus, which faces the cytoplasm, contains the specific sorting and retention signals required for NIS expression at the basolateral plasma membrane. In patients with dyshormonogenic congenital hypothyroidism, over thirty pathogenic variants in the NIS-coding SLC5A5 gene have been identified. The functional characterization of NIS variants identified in patients with loss-of-function has provided mechanistic information about the transporter. Given the importance of NIS in thyroid physiology, we recently developed a machine learning-based NIS-specific variant classifier with the goal of improving the prediction of missense NIS variant pathogenicity.

We used targeted next-generation sequencing to look for pathogenic variants in the SLC5A5 gene in a group of nine paediatric patients with dyshormonogenic congenital hypothyroidism suspected of being caused by an iodide transport defect based on the absence of 99mTc-pertechnetate accumulation in the thyroid gland. Surprisingly, no pathogenic SLC5A5 gene variants were found. As a result, we expanded our study to include a comprehensive panel of 16 other known causative congenital hypothyroidism genes. The cryo-electron microscopy 3D [4,5] structure of the human TG dimer has recently revealed that the monomers are intertwined, with each monomer entangled and revolving around the central ChEL dimer, which interacts with the Arm and Core domains of the same monomer, as well as the NTD of the partner monomer, which involves the E domain. Using the web-based molecular visualisation platform Mol* Viewer.

Conclusion

We used targeted next-generation sequencing to look for pathogenic variants in the SLC5A5 gene in a group of nine unrelated patients who had permanent dyshormonogenic congenital hypothyroidism and were suspected of having an iodide transport defect. Surprisingly, we found no pathogenic variants in the SLC5A5 gene to account for the genetic basis of thyroid disease. We recently reported a Sanger sequencing-based study that also assessed the presence of pathogenic SLC5A5 gene variants in a study cohort of four patients suspected of congenital iodide transport defect, but we only found the homozygous synonymous c.1326A>C variant, which resulted in aberrant NIS pre-mRNA splicing in one of the study cohort's patients.

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