Novel homozygous mutation in the sodium/iodide symporter (NIS) gene highlighted by next generation sequencing (NGS) in a patient with congenital hypothyroidism

Isabelle Oliver-Petit[1] , Isabelle Gennero[2,3], Frédérique Savagner[2, 3]

[1]Unité d'endocrinologie, hôpital des enfants; [2]Laboratoire de biochimie, IFB, Purpan & [3]Université Paul Sabatier, TOULOUSE, France

Nothing to disclose

Background

The ability to actively concentrate iodide actively is a specific feature of the thyroid gland. This function is mediated by the sodium iodine symporter (NIS), a glycoprotein located in thyrocytes'membrane.

Iodide transport defect (ITD) du to NIS anomalies can result in hypothyroidism with variable degree of goiter and low to absent radio iodide uptake. Mutations in SLC5A5 gene encoding NIS are reported to be a rare form of dyshormonogenesis congenital hypothyroidism (CH), with autosomal recessive inheritance pattern.

SLC5A5 gene is formed by 15 exons but unfortunately,, no medical lab in Europe is able to propose its routine analysis Sanger sequencing.

Objective and Method

- To explore a patient with CH and compatiblephenotype with NIS defect.
- Genomic DNA was explored by next generation sequencing (NGS) methode targeting 18 genes (SLC5A5 included) involved in thyroid dyshormonogenesis .

Clinical case & Result

- A boy was referred to our unitb for high TSH level on neonatal screening.

  At 10th day, **congenital hypothyroidism with eutopic thyroid gland** was confirmed with: TSH > 150 µui/ml; T4L 1.7 pg/ml [7.5-16]; T3L 1.5 pg/ml [2-4.2]; Thyroglobulin was high at 600 ng/ml;

  Ultrasound showed a large but normal-size thyroid gland 1.4 ml [0.4 - 1.42]; **Absence of radio-technetium uptake on scintigraphy**.

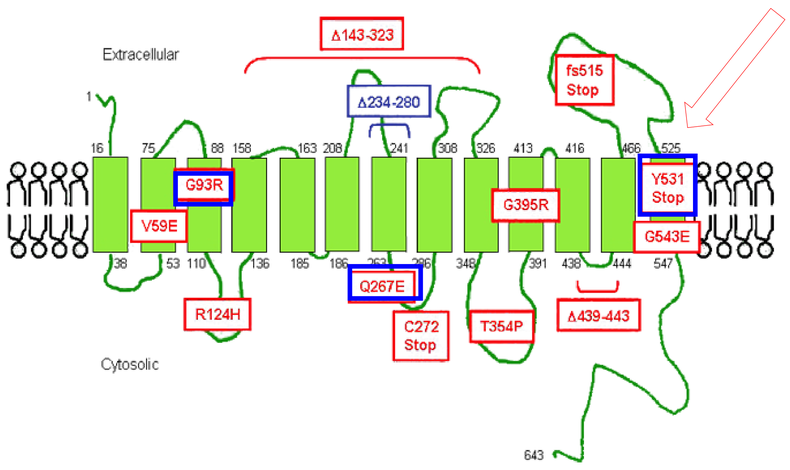
  No familial history for thyroid disease but baby's parents were **relatives second degree**.

` Thyroid hormone supplementation was immediately started with rapid normalisation of hormones' levels. Growth and psychomotor development are satisfactory for this child with a small homogeneous goiter on cervical ultrasonography survey after 3 years of age.

- The DNA analysis by NGS revealed **a homozygous C>G nonsense mutation in exon 13 of the SLC5A5 gene resulting in a premature stop at position 531 (p.Tyr531Stop)**.

- By the moment, 13 mutations have yet been described in the litterature ; all except one are homozygous mutations (see figure).This new mutation has been previously described in a context of compound heterozygous pattern but its impact on iodide transport or cell membrane targeting has not been clearly determined relative to the presence of the pathogenic other heterozygous mutation.

- **This homozygous mutation in the NIS gene leading to complete deletion of the 13th transmembrane and the carboxy-terminus part of the symporter underlines the role of this segment and of this Tyrosine 531 residue in the iodide trapping.**



The Sodium/Iodine Symporter (NIS) *is constitued by 643 amino-acids and 13 trans-membrane domains.*

Nearly all mutations yet described were homozygous (red square).

Compound heterozygous mutations described, with Y531 and G93R or Q276E (blue square)

Y531 is first described as homozygous mutation (Arrow)

Conclusion

We report the first patient with congenital hypothyroidism and severe ITD due to homozygous nonsense mutation (p.Tyr531stop) in NIS gene.

NGS targeting congenital hypothyroidism with eutopic gland appears as a high performance tool with diagnostic utility.

55ESPE 11--5-RFC

Thyroid

Isabelle Oliver

DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS 10-13 SEPTEMBER