IGSF1 mutation: treatment in the absence of symptoms?

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IGSF1 deficiency syndrome, what is already known...
- X-linked transmission, up to 15% of central congenital hypothyroidism
- Central hypothyroidism, macroorchidism (even in children), delayed puberty, ± hypoprolactinemia, ± transient GHD in childhood, excess weight and metabolic syndrome
- Variable expressivity ++

Clinical case
Male infant with symptoms of brain – lung – thyroid syndrome
→ Thyroid function tests: central hypothyroidism !
→ Normal hypothalamic-pituitary MRI results
Respiratory function: 2 episode of acute respiratory distress and then asthma

Genetic diagnosis at the age of 4 years

What is not known...
- Mechanisms explaining the characteristics of the syndrome
- Absence or mild symptoms are possible in central hypothyroidism
  - Compensatory mechanisms, such as an increase in deiodinase level to maintain a sufficient level of T3 ?
- Natural history of thyroid function in this syndrome ?
- Necessity of L-thyroxin treatment in the absence of symptoms ?

Conclusion
- Intra-familial expressivity is variable. Absence of symptoms or mild symptoms of hypothyroidism are possible, suggesting that there are probably compensatory mechanisms that remain to be discovered.
- Cognitive tests in these children should provide arguments for or against treatment in the absence of symptoms.
- Central hypothyroidism can worsen over time. Genetic tests are then essential to confirm diagnosis in family members.

Family investigation
3 brothers affected:
- One with severe symptoms
- One with mild symptoms
- One with no symptoms

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FT3 and FT4 levels for our 3 patients and the cases described by Roche, Clin Endocrinol. 2018
Symptoms of hypothyroidism (+)
No symptoms of hypothyroidism (−)