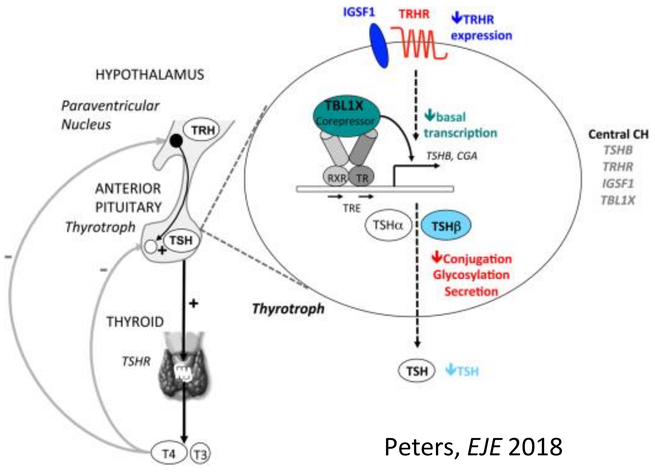
IGSF1 mutation: treatment in the absence of symptoms?

Sarah Castets (1), Julia Vergier (1), Alice Godefroy (2), Alexandru Saveanu (3), Patrick Collignon (4), Thierry Brue (3), Rachel Reynaud (2)
(1) CHU Timone Enfants, Marseille, France (2) Hôpital Saint Joseph, Marseille, France (3) : CHU La Conception, Marseille, France (4) Hôpital de Toulon, France



Peters, *EJE* 2018

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 ++

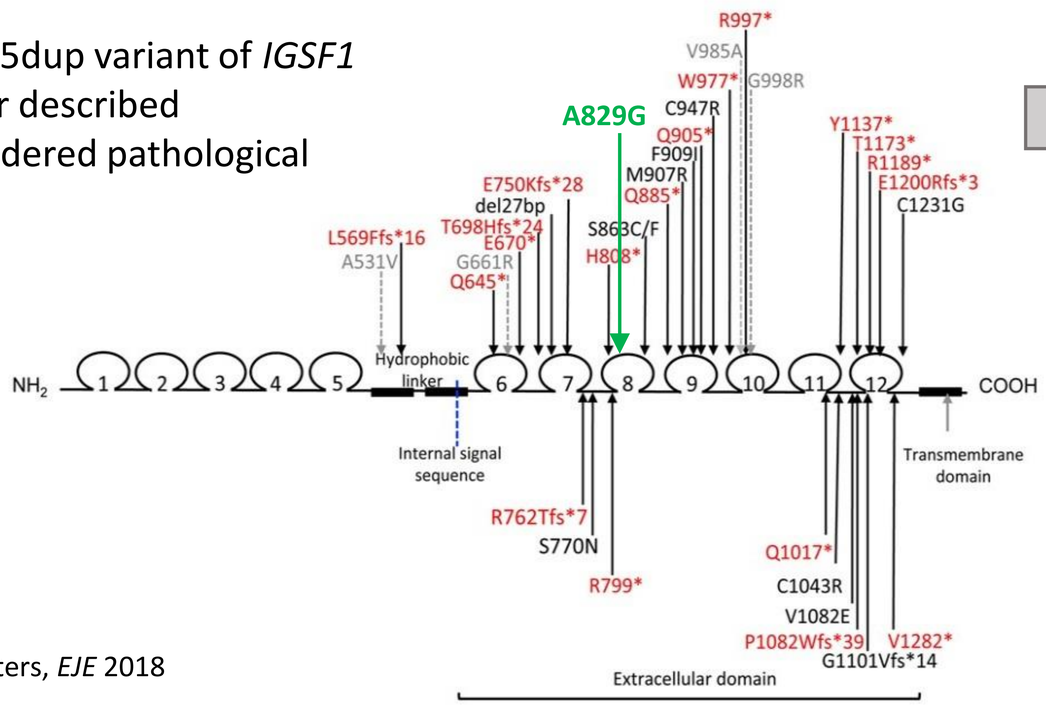
Clinical case

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

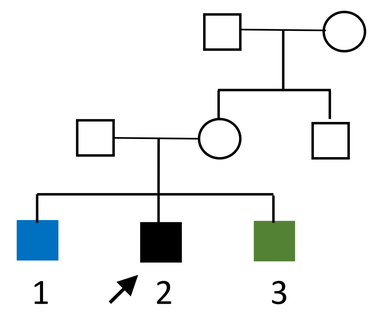
Genetic diagnosis at the age of 4 years

c.2485dup variant of *IGSF1*
Never described
Considered pathological



Peters, *EJE* 2018

Family investigation



3 brothers affected:

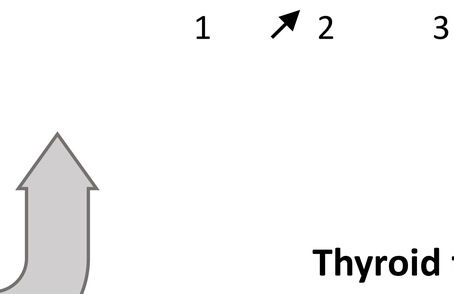
- **One with severe symptoms**
- **One with mild symptoms**
- **One with no symptoms**

Thyroid function test at diagnosis

	Age	TSH (mUI/l) (0,7 – 5,97)	T3 (pmol/l) (3,7 – 8,4)	T4 (pmol/l) (12 – 22)	Symptoms of hypothyroidism
1	6 years	2,79	4,3	9,2	
2	Neonate	3,8	1,56	6,2	Severe hypotonia
3	3 days	10,8	3,5	11,4	Slightly overweight
	9 months	1,67	5,6	8,2	

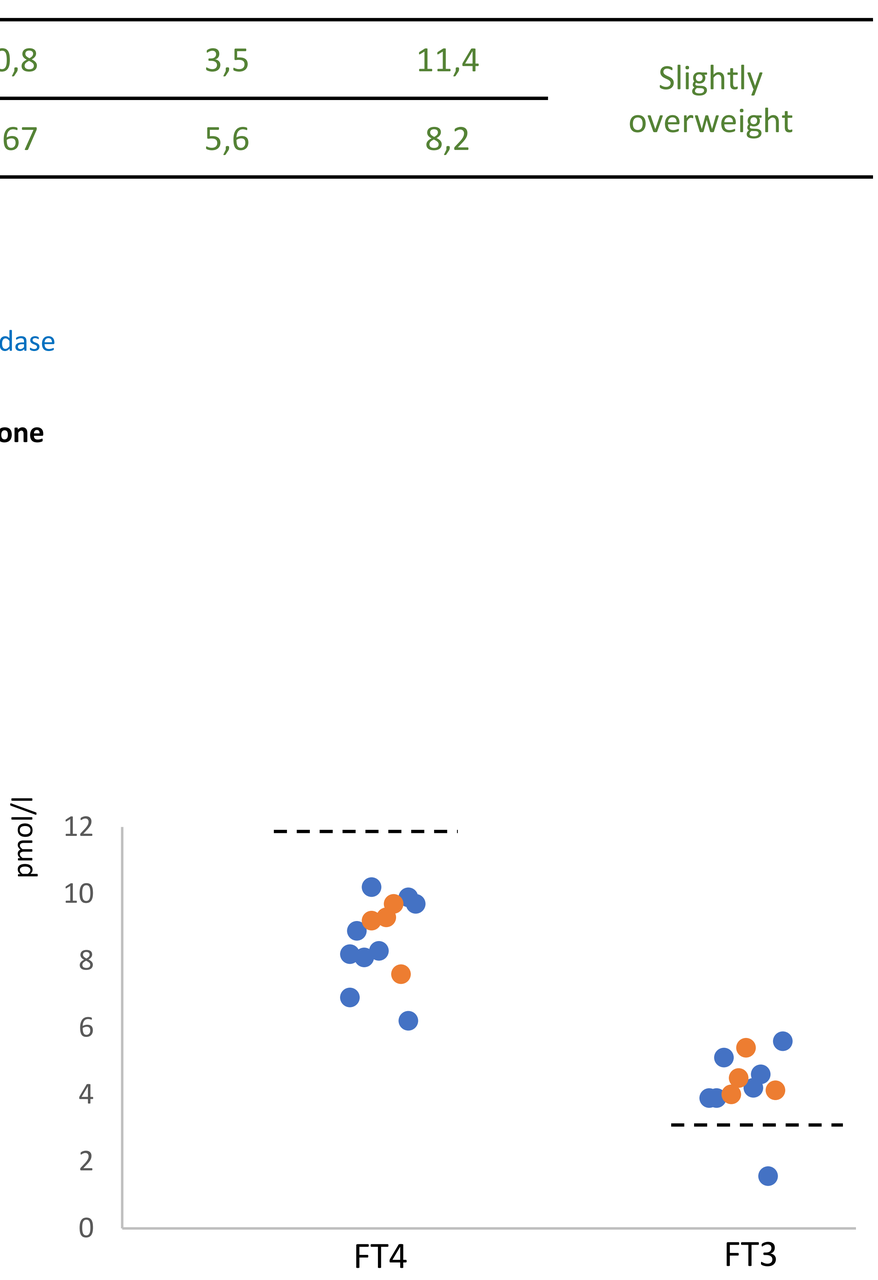
What is not known…

- 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.



FT3L and FT4 levels for our 3 patients and the cases described by Roche, *Clin Endocrinol.* 2018

Symptoms of hypothyroidism (●)
No symptoms of hypothyroidism (●)