

# A NOVEL MUTATION IN THE TTF-1 GENE IN A CHILD WITH BENIGN HEREDITARY CHOREA

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## INTRODUCTION

- ✓ Benign hereditary chorea (BHC) is a rare autosomal dominant disorder described as a non-progressive chorea of early onset
- ✓ Clinical manifestations of BHC can be single neurologic disorder (13%), brain and thyroid diseases (30%), or "brain-lung-thyroid syndrome" including neurological disorders, thyroid dysfunction and neonatal respiratory distress syndrome (50%) (Fig. 1).

## CASE REPORT

- XY, 18 months-old, was admitted to the Pediatric outpatient clinic because of motor delay and gait disorder
- He was the second son of healthy and non-consanguineous parents. Family history was uneventful
- Perinatal history was unremarkable for pulmonary problems and screening test for congenital hypothyroidism was normal

### Clinical Findings

- He had short stature (-1.99 SDS), normal weight (BMI 19.4 kg/m<sup>2</sup>), without significant dysmorphic features
- Neurological evaluation showed hypotonic and joint laxity, axial dystonia and choreic movements

### Laboratory and instrumental data

- No inherited metabolic disease was shown, array-CGH were normal, and IGF-1 levels (35 ng/ml) were at the normal lower range
- Thyroid function evaluation was suggestive of subclinical hypothyroidism (TSH 8.46 μIU/ml and fT4 11.1 pg/ml)
- Brain MRI showed mild abnormalities in peripheral regions, a large cistern and hippocampus' dysmorphisms

Neurological signs associated to thyroid dysfunction led us to hypothesize BHC

The thyroid transcription factor 1 gene (TTF-1, *cr.14q13.3*) molecular test identified a heterozygous substitution (**Pro291Arg**)

## CONCLUSIONS

- The TTF-1 gene is essential for the organogenesis of lungs (Fig. 2), thyroid, and development of the basal ganglia
- Genotype/phenotype association can be extremely variable because of many clinical features of the disease
- Thyroid dysfunction associated with hypotonia and choreic jerks induced to suspect this rare condition
- Our clinical case is peculiar because of a "de novo" mutation and choreic jerks were subtle and were not the main clinical feature

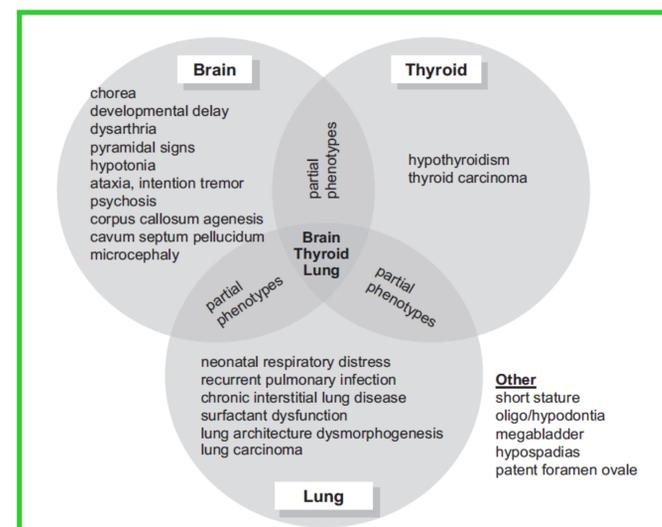


Fig. 1 Phenotypic presentations of the "Brain-thyroid-lung syndrome"

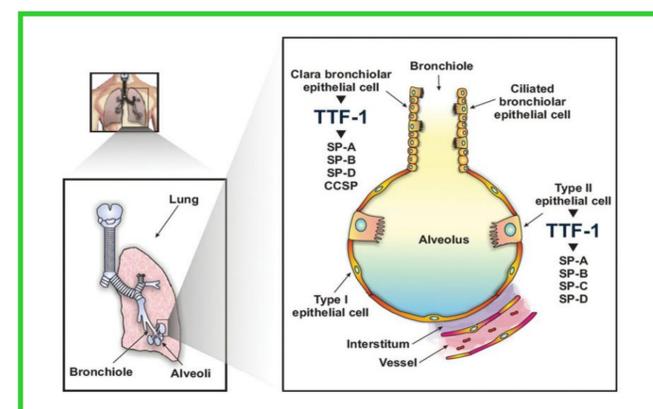
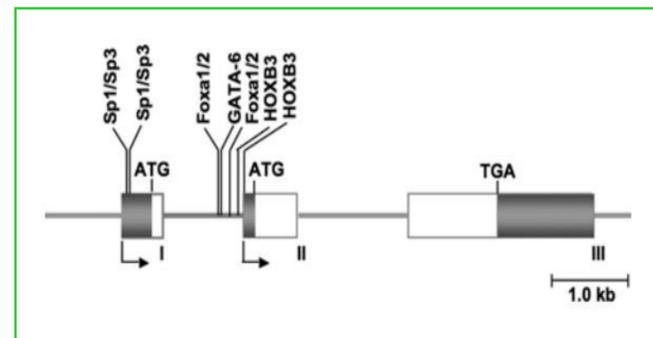


Fig. 2 TTF-1 regulates the expression of surfactant apoproteins (A,B,C)

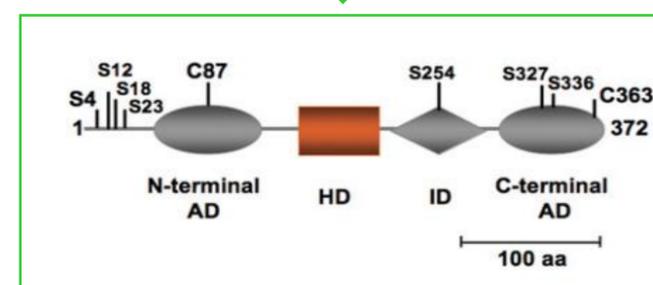


## TTF-1 gene

Exons are represented by rectangles and introns and 5 and 3 flanking regions are represented by lines.

## TTF-1 protein organization

The N- and C-terminal activation domains (AD), the homeodomain (HD) and the inhibitor domain (ID).



Authors have nothing to disclose