TWO NOVEL MUTATIONS OF THE LHX3 GENE ASSOCIATED WITH A SEVERE PHENOTYPE INVOLVING ENDOCRINE, NERVOUS AND SKELETAL SYSTEMS

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INTRODUCTION

LHX3, a member of the LIM-homeodomain transcription factors family, regulates pituitary development in vertebrates and the maintenance of mature anterior pituitary cells. Nineteen mutations in LHX3 gene have been reported in HGMD database, in homozygous and compound heterozygous patients. The phenotype may present with pituitary dysfunction only or with syndromes involving also nervous and skeletal systems. The MRI images include aplasia or hypoplasia of pituitary, hypointensity resembling microadenoma, enlargement with hyperintense signal, while in 10% of cases MRI is normal. Heterozygous family members are unaffected.

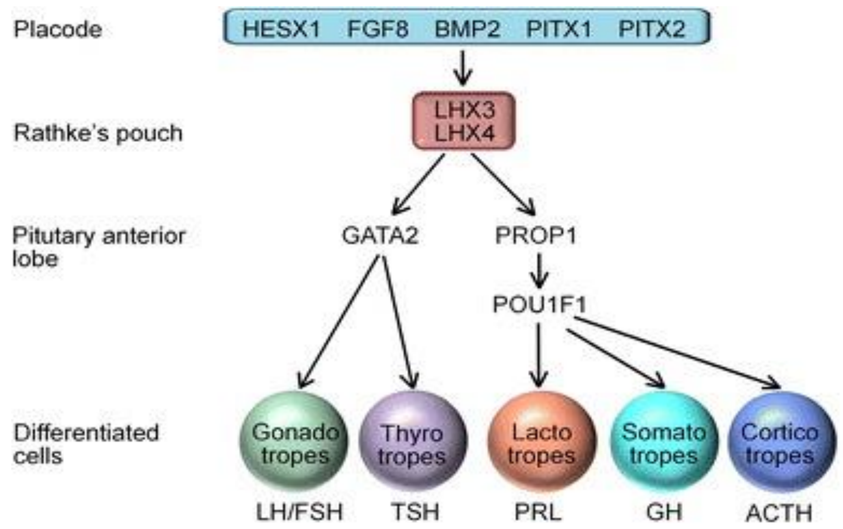

Fig. 1 A simplified scheme of the development cascade representing the main transcription factors expression during pituitary development . Pituitary cell lineages are determined by the activation or repression of each transcription factor. LHX3 participates in the pituitary cell differentiation and maturation process (Ramzan, 2017)

CLINICAL CASE

Our patient is a girl, term born. AGA for weight and length. After birth the child presented a severe respiratory distress. Considering her condition of therapy-refractory hypotension, pituitary hormonal investigations were performed at one month of age and a condition of panhypopituitarism was confirmed. Replacement therapy with hydrocortisone, levothyroxine and growth hormone was started. Brain MRI showed a loss of the adenohypophysis enhancement after-contrast.
At 6 months a psychomotor delay and a short neck with abnormal head and neck rotation were evident. At 4 years a left hip dislocation was partially surgically corrected and at 11 years a definitive vertebral fixation surgery for a severe scoliosis was performed. Since she was 3 years old she used hearing aids and at the age of 9 a cochlear implant was applied. At 8 years a surgical correction of a right eye strabismus was also performed. Despite GH therapy the patient had poor growth at -2.5 SDS. At the age of 11 she reached the 3rd percentile probably due to the scoliosis correction surgery. At 12 years the girl started estrogen therapy and at 13 years of age she has now reached the 10th percentile with the bone age still delayed of 3 yrs. The parents have a silent phenotype.

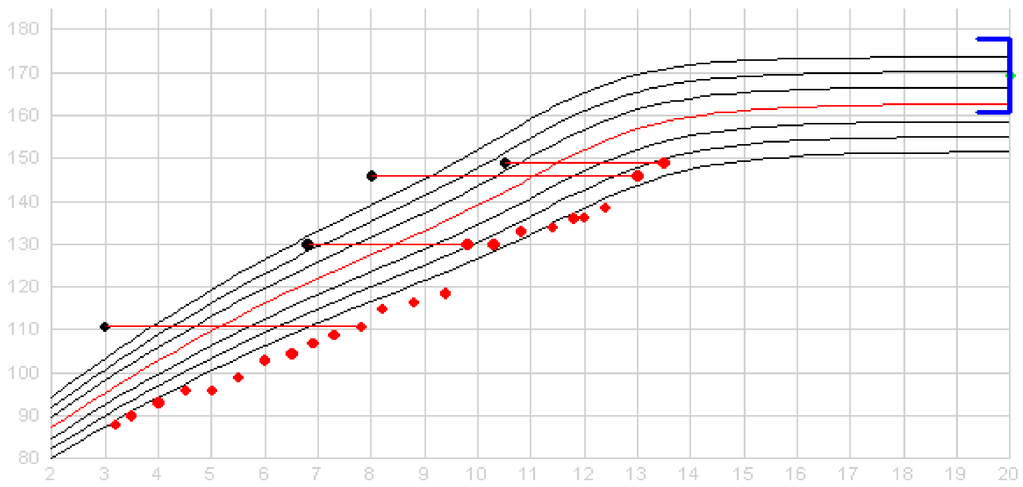

Fig 3 Cacciari italian Growth Chart – Stature for age

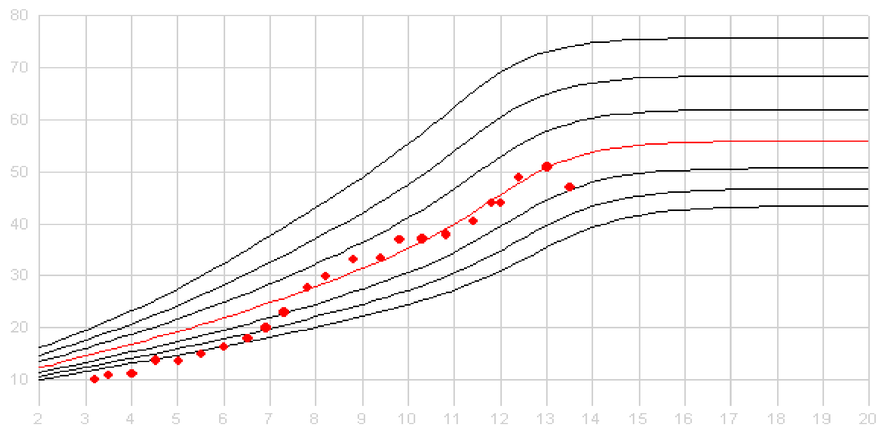

Fig 4 – Cacciari italian Growth Chart – Weight for age

RESULTS

The NGS analysis of genes known associated with panhypopituitarism pointed out two new variants of LHX3 gene (NM_014564), not described in literature so far: c.G641C (p.R214P) located in exon 5 of the gene, inherited from the mother, and c.G359A (p.C120Y) located in exon 3, inherited from the father. These SNPs are located in a mutational hot spot, established functional domain without benign variation; multiple lines of computational evidence support a deleterious effect on the gene or gene product.

CONCLUSIONS

We conclude that the two variants pointed out from our analysis are good candidates to explain the complex proband phenotype. We are planning a functional study to validate this hypothesis..

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