**INTRODUCTION AND OBJECTIVES**

LHX (LIMH1, IGF1 and MEC-3) domain transcription factors LHX4, LHX3, LHX2 or ISL1 are essential in pituitary ontogenesis (1, 2). Mutations in some of those genes result in combined pituitary hormone deficiency (CPHD) (3), and are often associated with variable pituitary and extra-pituitary anomalies on MRI. LH4X mutations are rare in humans. They result in large intra- and inter-familial variability of the phenotype (4, 5). The nature of the deficient pituitary hormones is variable. The extra-pituitary anomalies could be absent. On the other hand, ectopic posterior pituitary, abnormal sella turcica shape or abnormal corpus callosum has been reported (6).

Only eight LHX4 mutations transmitted as an autosomal dominant trait have been reported in the literature (4-8, 15).

**METHODS**

Targeted resequencing was performed using TruSight One Sequencing Panel kit (Illumina, San Diego, CA, USA). The TruSight One Sequencing Panel contains probe sets for enrichment and analysis of ~4,800 clinically relevant genes, targeting 12Mbp of the human genome. Sequencing libraries were prepared according to Illumina protocol and sequenced on NextSeq 550. An Illumina MiSeq di/di shallow sequencing using paired-end 150bp sequencing reads. Raw sequence data were aligned against reference genome specified in the manifest file using MiSeq Reporter software. Each single variant was reported in the VCF output file which was used for the variant calling and filtering via Variant Studio software (Illumina). More comprehensive analyses were done for the variants with a global frequency under 1% according to the 1000 genomes database (http://www.1000genomes.org) and the ExAC database (http://exac.broadinstitute.org), particularly those in the genes implicated in growth hormone deficiency. Variants with known pathogenic clinical significance according to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and LOVD (http://www.lovd.nl/3.0/home) were also thoroughly investigated. PCR amplification and Sanger DNA sequencing of the exon 3 from LHX4 gene were performed for the confirmation of the c.280C>T (p.Arg94Cys) variant in the patient and for the analysis of the parents.

**RESULTS**

The first described mutation of the LH4X gene in humans was c.687G>C (15)(Table 1), resulting in multiple pituitary deficiencies: GH, TSH, ACTH. This affected multiple members of the family in which only one member was fertile. There were multiple MRI pituitary anomalies: hypoplasia of the pituitary, a small sella turcica, and craniopharyngioma.

In pituitary stalk interruption syndrome a mutation of LH4X gene was reported (5). Early GH and TSH deficiencies, later onset ACTH deficiency, decreased IGF1, and elevated TSH were noted in the W204X mutation (16). Multiple pituitary deficiencies, small sella and craniopharyngioma (i.e., sellar cyst) were noted in the missense mutation (P367E) of the LHX4 gene (9). In addition, there was severe respiratory disease and hypoglycemia was present in both.

**CONCLUSIONS**

The genetic defects of LH4X have a high variability in clinical manifestations even in the same family, no clear genotype-phenotype correlation and the phenotype may include extra-pituitary manifestations. Other genetic and/or environmental factors modify the phenotype.