A novel LHX4 mutation is associated with hypogonadotropic hypogonadism, not combined pituitary hormone deficiency

Masaki Takagi1,2, Takashi Daitsu3, Chihakahiko Numakura4, Takeshi Sato5, Satoshi Narumi2, and Tomonobu Hasegawa2
1 Department of Endocrinology and Metabolism, Tokyo Metropolitan Children’s Medical Center 2 Department of Pediatrics, Keio University School of Medicine 3 Department of Pediatrics, Yamagata City Hospital Saiseikan 4 Department of Pediatrics, Faculty of Medicine, Yamagata University

Disclosure statement: The authors have declared no conflicts of interest.

Take Home Message
We showed for the first time that LHX4 mutation is associated with hypogonadotropic hypogonadism (HH), not combined pituitary hormone deficiency (CPHD).

Backgrounds
Several transcription factor genes have been linked to the pathogenesis of CPHD, including PROK1f1, PROP1, HESX1, LHX3, OTX2, SOX2, SOX3, GLI2, and LHX4.

In addition to these genes, some causative genes for Kallmann syndrome (KS), which is defined by HH with anosmia, have been identified in a small number of CPHD and septo optic dysplasia (SOD)1,2.

On the other hand, mutations in HESX1, SOX3, responsible for CPHD have been identified in a small number of HH.

These findings strongly suggest that the genetic overlap between CPHD, SOD, and KS/HH is significant.

Objectives
We report an infant clinically diagnosed as HH with a novel missense mutation in LHX4 (R221W).

Materials & Methods
Case Report
A 2-month-old boy was referred because of micropenis (stretched penile length 1.0 cm) with intrascrotal testes (right 1 mL, left 1 mL).

Hormone assays revealed very-low plasma testosterone concentrations (0.06 ng/mL). LHRH stimulating test performed at the age of 3 months (minipuberty) revealed LH peak 7.3 mIU/mL, and FSH peak 20.7 mIU/mL, suggesting pre-pubertal response.

Plasma concentrations of thyroxine and insulin-like growth factor-1 concentrations (0.06 ng/mL). LHRH and hCG stimulating test showed normal GnRH response.

He was diagnosed as HH clinically. He responded well to testosterone enanthate therapy (im 25 mg every 4 wk for three doses).

At the last examination at age 20 months, his height and weight were -0.2 SD, and +1.3 SD, respectively.

Discussion
1. We characterized a novel mutant (R221W) of the LHX4 transcription factor that is associated with HH. Arginine 221 is a highly conserved amino acid located immediately 3’ of the homeodomain, suggesting that substitution of arginine 221 to tryptophan, which is predicted to lose a residue-DNA contact, results in defective interactions with DNA.

2. We showed for the first time that LHX4 mutation is associated with HH, not CPHD. This unique and/or mild phenotype could be due to residual LHX4 activity. The findings in this patient emphasize the importance of testing for LHX4 mutations in HH individuals. This study extends our understanding of the phenotypic features, molecular mechanism, and developmental course associated with mutations in LHX4.

Contact: mtakagi1027@hotmail.com

Results
R221W had reduced transactivation, and had no dominant negative effect (FIG.A). Subcellular localization revealed no significant difference between WT and R221W (FIG.B). WT LHX4 showed specific binding to the elements, which was competed by excess amount of cold competitors. EMSA experiments showed that the R221W LHX4 had reduced DNA-binding affinity (FIG.C).

A. Transactivation assays

B. Subcellular localization

C. EMSA experiments

Disclosure statement: The authors have declared no conflicts of interest.

Poster presented at: Puberty and Neuroendocrinology
Masaki Takagi
DOI: 10.3201/pso.eu.54espe.2015

1 Reynaud et al. 2012 J Clin Endocrinol Metab
2 McCabe et al. 2013 J Clin Endocrinol Metab
3 Newborn et al. 2013 Fertil Sterili
4 Izumi et al. 2014 Fertil Sterili

1. We characterized a novel mutant (R221W) of the LHX4 transcription factor that is associated with HH. Arginine 221 is a highly conserved amino acid located immediately 3’ of the homeodomain, suggesting that substitution of arginine 221 to tryptophan, which is predicted to lose a residue-DNA contact, results in defective interactions with DNA.

2. We showed for the first time that LHX4 mutation is associated with HH, not CPHD. This unique and/or mild phenotype could be due to residual LHX4 activity. The findings in this patient emphasize the importance of testing for LHX4 mutations in HH individuals. This study extends our understanding of the phenotypic features, molecular mechanism, and developmental course associated with mutations in LHX4.