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## Introduction

- Isolated gonadotropin-releasing hormone (GnRH) deficiency (IGD) is caused by a deficiency in GnRH production, secretion or action. IGD is a highly heterogeneous disorder with wide phenotypic spectrum including Kallmann syndrome (KS) with anosmia and normosmic idiopathic hypogonadotropic hypogonadism (nIHH).
- Over the last 20 years, significant progress has been made in the understanding of the molecular genetics of IGD. More than 30 different causative genes have been identified in several studies.
- However, there are no data on the prevalence, clinical characteristics, and molecular spectrum in Korea.

## Objectives

- This study was performed to investigate the phenotypic and genotypic spectrum of patients with IGD in Korean population.

## Methods

- This study included 41 patients from 40 families diagnosed between January 1995 and December 2017.
- Clinical and endocrine characteristics were retrospectively analyzed including cryptorchidism, micropenis, anosmia, associated anomalies, family history, and laboratory findings.
- Mutation analysis was performed using targeted gene panel for known 69 IGD genes (n = 33) or whole exome sequencing (n = 8)

## Results

### Clinical characteristics at baseline

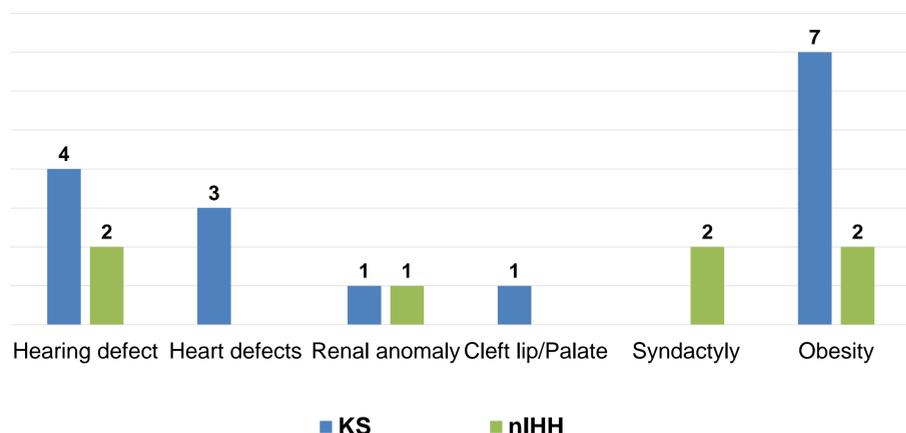
- KS was predominant in men (M:F = 24:0) compared to patients with nIHH (M:F= 10:7).
- The mean age at presentation was 14.5 ± 5.0 years (range, 4.7–21.3 years) in KS including two prepubertal males with isolated anosmia and 17.5 ± 2.2 years (range, 13.7–22.5 years) in nIHH (P = 0.015).

**Table 1.** Baseline characteristics of patient with IGD

	KS (n = 24)	nIHH (n = 17)	P value
Sex	M : F = 24 : 0	M : F = 10 : 7	
Mean age at presentation (year)	13.3 ± 6.4	16.6 ± 2.1	0.109
Mean age at diagnosis (year)	14.5 ± 5.0	17.5 ± 2.2	0.053
Micropenis (male)	17/24	5/10	0.181
Cryptorchidism (male)	6/24	2/10	0.754
Hypospadias (male)	1/24	0	0.512

- Micropenis was the most common manifestation of male patient of IGD (22/34, 64.7%), cryptorchidism(8/34, 23.5%) and hypospadias(1/34, 2.9%) were followed.
- Two pre-pubertal males presented with anosmia and aplasia of the olfactory bulbs at 8.1 and 5.8 years, respectively.
- The other patients presented with delayed puberty or primary amenorrhea.

### Non-reproductive features of KS and nIHH



**Fig. 1.** Non-reproductive features of patients with KS and nIHH

- Non-reproductive features were found in 9 patients with KS [hearing defect (n = 4), renal anomaly (n =1), cleft lip/palate (n =1), heart defects (n = 3)] and 5 patients with nIHH [hearing defect (n = 2), renal anomaly (n =1), syndactyly (n = 2)].

### Endocrinological characteristics

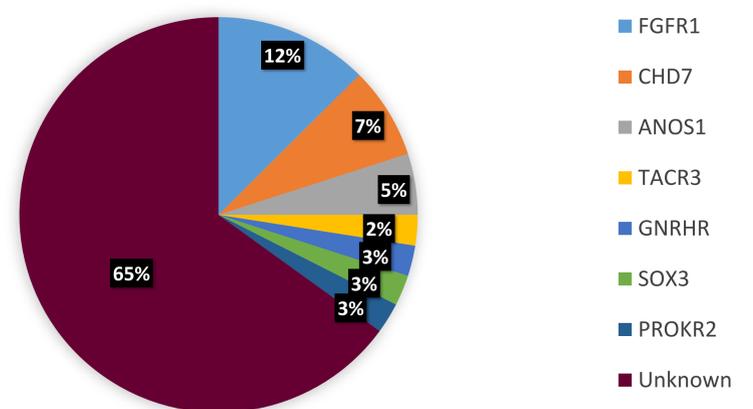
- GnRH stimulation test was performed at the time of diagnosis; peak LH and FSH levels were 3.86 ± 3.42 mIU/mL and 3.9 ± 2.24 mIU/mL, respectively.
- After hormone replacement therapy, penile length (range, 3.5-8.5cm), testis volume (range, 1.5-8cc), pubic hair (range, stage 1-6.5) was improved.

**Table 2.** Endocrinologic features and clinical outcome of patients with IGD

	KS	nIHH	P value
Basal LH (mIU/mL)	1.06 ± 0.76	0.95 ± 0.69	0.497
Peak LH (mIU/mL)	3.86 ± 3.42	3.61 ± 4.06	0.863
Basal FSH (mIU/mL)	0.93 ± 0.7	1.56 ± 2.67	0.988
Peak FSH (mIU/mL)	3.9 ± 2.24	4.59 ± 4.29	0.987
Estradiol (pg/mL) (female)		19.7 ± 12.4	
Testosterone (ng/mL) (male)	0.73 ± 2.3	0.47 ± 0.86	0.714
Penile length (cm)	3.48 ± 1.45	3.67 ± 1.41	<0.001
Testis volume (mL)	1.77 ± 1.23	2.0 ± 0.82	<0.001
Pubic hair (Tanner stage)	1.33 ± 0.70	1.3 ± 0.48	<0.001

### Molecular characteristics

- Among 40 families, rare sequence variants were identified 8 probands with KS and 7 probands with nIHH, respectively. *FGFR1* (5/40, 12.5%) was the most common, followed by *CHD7* (3/40, 7.5%), *ANOS1* (2/40, 5%), *TACR3* (1/40, 2.5%), *GNRHR* (1/40), *SOX3* (1/40), and *PROKR2* (1/40).



**Fig. 2.** Rare sequence variants identified in 40 probands with IGD

## Conclusions

- KS was predominant in males, and they presented earlier than those with nIHH.
- The prevalence of non-reproductive features were not different between patients with KS and nIHH.
- Two prepubertal males with anosmia should be followed up to initiate timely hormonal replacement therapy.
- Overall, genetic diagnosis was possible in 37.5% of probands with IGD with 13 pathogenic or likely pathogenic variants and two variants of uncertain significance.

## References

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## Disclosure statement

The authors have nothing to disclose.