Case report

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Familial male-limited precocious puberty due to an activating mutation of the LHCGR: a case report and literature review

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Familial male-limited precocious puberty (FMPP) is a rare form of gonadotropin-independent precocious puberty that is caused by an activating mutation of the *LHCGR* gene. Herein, we report a case of FMPP with a mutation of the *LHCGR* gene in a Korean boy with familial history of precocious puberty through 3 generations. A 16-month-old boy presented with signs of precocious puberty, including pubic hair, acne, and increased growth velocity. The patient's grandfather and father had a history of precocious puberty and profound short stature. On physical examination, the patient had prepubertal testes with pubic hair development appropriate for Tanner stage II. The stretched penile length was 7 cm (>2 standard deviation score), and observed bone age was that of a 4-year-old boy. Laboratory findings showed high serum testosterone (5.74 ng/mL [appropriate for Tanner IV–V]; normal range, <0.05 ng/mL) with suppressed luteinizing hormone (<0.07 mIU/mL) and normal serum level of follicular stimulating hormone (0.56 mIU/mL; normal range, 0.38–1.11 mIU/mL). Genetic testing revealed a pathogenic variant of *LHCGR* (c.1730 C>T (p.Thr577Ileu)), confirming FMPP. Bicalutamide and anastrozole were administered, and pubertal progression was sufficiently suppressed without any specific side effects. To our knowledge, this is the first case of genetically confirmed FMPP in Korea.

Keywords: Familial male-limited precocious puberty, *LHCGR*, Anastrozole, Bicalutamide

Highlights

- Familial male-limited precocious puberty (FMPP) is a rare disorder characterized by early onset gonadotropin-independent precocious puberty. This report presents an extremely rare case of FMPP with an activating mutation of the *LHCGR* gene in a Korean boy who presented with precocious pubertal development at 16 months of age and a positive familial history of precocious puberty.

Introduction

Familial male-limited precocious puberty (FMPP; OMIM #176410) is a very rare cause of gonadotropin-independent precocious puberty and is exclusively expressed in males. FMPP is caused by activating mutations of the luteinizing hormone/chorionic gonadotropin receptor (*LHCGR*) gene that are inherited in an autosomal dominant manner. This results in excessive testosterone production by the Leydig cells despite low luteinizing hormone (LH) and follicular stimulating hormone (FSH) levels. This activating mutation in *LHCGR* affects only males because activation of the LH receptor alone is sufficient to stimulate steroidogenesis

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in Leydig cells. In females, co-activation of the FSH receptor is definitely required to stimulate granulosa cells to synthesize aromatase, which converts androgens produced by the thecal cells to estradiol, but the precise underlying mechanism remains elusive.[1,2]

In affected males, early signs of precocious puberty usually appear at 2–4 years of age.[1,3] Rapid growth and bone age advancement result from the conversion of androgens to estrogens by the enzyme aromatase. Without treatment, rapidly progressive precocious puberty and accelerated skeletal maturation result in compromised final adult height.[4] Diagnosis of FMPP is confirmed by identifying an activating mutation in the *LHCGR* gene. The goals of treatment are to suppress pubertal progression by reducing the effects of testosterone and to increase final adult height by inhibiting the aromatization of testosterone to estrogen.[3-5]

In this report, we describe a boy with a familial history of precocious puberty confirmed by a mutation of the *LHCGR* gene. To the best of our knowledge, this is the first case of genetically confirmed FMPP in a Korean boy.

Written informed consent for publication of this report was obtained from the patient's parents.

Case report

A 16-month-old boy was brought to our outpatient clinic with complaints of premature pubic hair development, acne, and accelerated linear growth, which was observed by the patient's parents at the age of 12 months. The patient was born at 37^{+2} weeks of gestation by cesarean section with a birth weight of 2.45 kg (-1.7 standard deviation score [SDS]). The patient was the first baby of fraternal twins and had a healthy twin sister. The patient's grandfather and father had a history of precocious puberty and profound short stature (height of grandfather and father: 148 cm and 158 cm, respectively). Upon physical examination, the patient's height and weight were 83 cm (+1.2 SDS) and 14.3 kg (+2.8 SDS), respectively. The testicular volume was 2 mL bilaterally, and pubic hair development was appropriate for Tanner stage II (Fig. 1). The stretched penile length was 7 cm (>2 SDS). The patient had an oily face with acneiform eruptions without any dysmorphic features, gynecomastia, or palpable abdominal masses. Cafe-au-lait spots and hyperpigmentation were not observed. The patient's bone age was estimated by the Greulich-Pyle method[6] and was significantly advanced to 4 years of age.

Laboratory findings showed extremely high serum testosterone (5.74 ng/mL [appropriate for Tanner IV–V]; normal range, <0.05 ng/mL), suppressed LH (<0.07 mIU/mL; normal range, 0.02–0.15 ng/mL), normal serum level of FSH (0.56 mIU/mL; normal range, 0.38–1.11 mIU/mL), slightly elevated α-fetoprotein (14.1 ng/mL; normal range, 0–10 ng/mL), and normal serum level of β-human chorionic gonadotropin (<0.2 mIU/mL, normal range, <5 mIU/mL). Adrenocorticotropic hormone (25.4 pg/mL; normal range, 10–60 pg/mL), cortisol (10.44 μg/dL; normal range, 3–21 μg/dL), 17-hydroxyprogesterone (1.96 ng/mL; normal range, 0.03–9 ng/mL), androstenedione (<0.3 ng/mL; 0.08-0.5 ng/mL), and dehydroepiandrosterone sulfate (19.1 μg/dL; 5–57 μg/dL) were all within the normal infant range. A gonadotropin-releasing hormone (GnRH) stimulation test did not stimulate gonadotropin (peak LH and FSH, 0.52 and 6.69 mIU/mL, respectively). Magnetic resonance imaging of the brain and ultrasonography of the scrotum and adrenal gland were all normal. Mutation analysis of the *LHCGR* gene identified a heterozygous mutation, c.1730 C>T (p.Thr577Ileu), which was previously reported in a patient with FMPP.[7] Familial genotyping confirmed a normal genotype from the mother, but the same pathogenic variant of *LHCGR* was identified from the father. The patient was finally diagnosed with FMPP based on clinical, laboratory, and genetic findings.

A combination of antiandrogen treatment with bicalutamide (25 mg/day) and aromatase inhibition with anastrozole (1 mg/day) was initiated,[8] and the patient was followed up every 1–3 months. Serum LH and FSH levels were maintained within prepubertal ranges during the follow-up period (Table 1). Despite persistently elevated testosterone level (6.79–8.85 ng/mL, Table 1), pubertal progression was sufficiently suppressed, showing a decreased stretched penile length to 6 cm, pubic hair to Tanner stage I, and resolved acneiform eruptions. The patient's growth velocity decreased from 2.1 cm/mo to 14 cm/10 mo (Fig. 2). At 27 months of age, the patient's bone age, as estimated by the Greulich-Pyle method, was 4.8 years. No specific side effects were observed, and aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and creatinine levels were all normal (Table 1).

Written informed consent was obtained from the patient's parents to publish this case report.

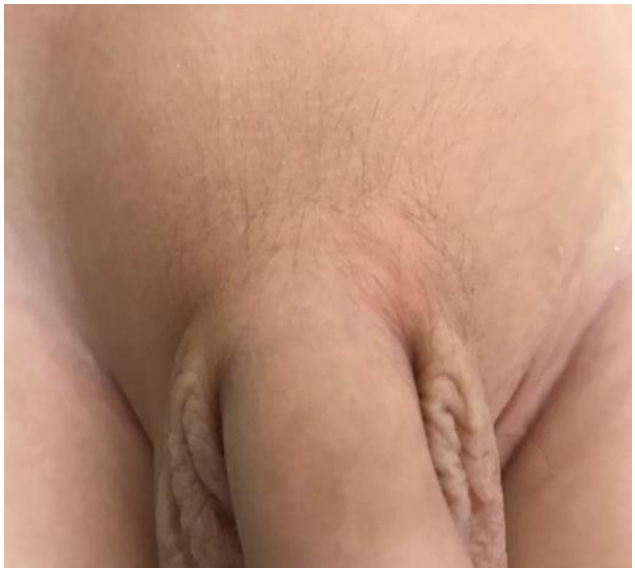

Fig. 1. A 16-month-old boy with premature pubic hair development. The patient's pubic hair at 16 months of age was appropriate for Tanner stage II.

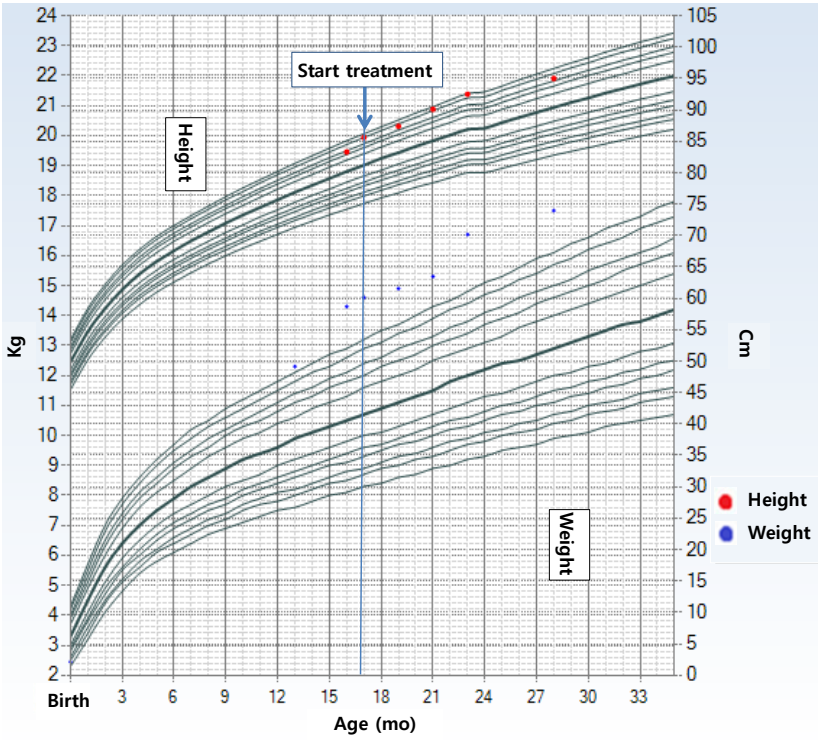

Fig. 2. Growth curve of the patient. In the short-term follow-up, the patient's growth velocity decreased from 2.1 cm/mo to 14 cm/10 mo.

Discussion

In this report, we describe an extremely rare case of FMPP with a mutation of the *LHCGR* gene in a Korean boy who presented with precocious puberty at 16 months of age and a family history of precocious puberty through 3 generations. To our knowledge, this is the first case of genetically confirmed FMPP in Korea.

LHCGR is a member of a subfamily of G protein-coupled receptors characterized by a large N-terminal extracellular domain containing several leucine-rich repeats. The gene comprises 11 exons, spanning approximately 80 kb, mapped on chromosome 2p16.3.[2] The gain-of-function mutation of *LHCGR* causes FMPP with autosomal dominant inheritance, whereas the loss-of-function mutation results in Leydig cell hypoplasia with hypergonadotropic hypogonadism of males or 46, XY disorder of sex development. The mutations are inherited in an autosomal recessive manner (OMIM *152790).

FMPP is one of the rarest causes of peripheral precocious puberty, exclusively affecting males. It was first described in 1981 by Schedewie et al.[1] in 2 brothers with rapid virilization, increased bone age, and advanced spermatogenesis. Variable clinical features of precocious puberty and advanced bone age were observed in subsequent reports.[8-16] The characteristics and pathogenic variants of patients with FMPP in recent case reports are summarized in Table 2. The onset age of symptoms ranged from 6 months to 6.6 years, and only 2 patients were younger than the patient in the present case.[8,11] Among the 7 unrelated patients who underwent parental genotyping, mutations were inherited from 3 affected fathers and 3 asymptomatic carrier mothers, and 1 patient had a *de novo* mutation (Table 2).

The mutation spectrum of the *LHCGR* gene causing FMPP is heterogeneous; however, activating mutations that were identified in boys with FMPP, including that in our case, are primarily located in exon 11, which encodes transmembrane helices.[17] An activating mutation either disrupts the inactive state or stabilizes the active-state conformation of the *LHCGR* protein, resulting in persistently elevated *LHCGR* signal transduction in testicular Leydig cells, with excessive testosterone production.[2]

The therapeutic goals of FMPP are to suppress pubertal progression and to delay epiphyseal fusion to increase final adult height.[3] Virilization can be abated by reducing the peripheral effects of testosterone on the androgen receptor or inhibiting testosterone synthesis. Epiphyseal fusion can be delayed by inhibiting the conversion of testosterone to estrogen or by blocking the action of estrogens at the epiphyses. Long-acting GnRH agonists were the primary treatment before the discovery of the molecular mechanism of FMPP; such agonists were ineffective as they could not suppress the action of elevated testosterone.[18] After the pathophysiology was better understood, antiandrogen drugs, such as medroxyprogesterone acetate, cyproterone, and ketoconazole, were used. These medications decreased testosterone secretion, growth velocity, and skeletal maturation but showed limited efficacy in improving final

Table 2. Summary of phenotypes and genotypes in patients with familial male-limited precocious puberty in recent case reports

No.	Study	Age of onset	Symptoms at presentation	Clinical and laboratory findings	Family history	Mutation in the *LHCGR* gene	Family member with mutation	Treatment (dose) (duration of treatment)	Outcome
1	Yuan et al.[12] (2022) (China)	2.6 Years	Enlarged penis, pubic hair, accelerated growth, enlarged testes at 3.8 years	BA 9 years, elevated serum testosterone (231 ng/dL), pubertal response to GnRH ST at 3.8 years	Yes (father's short stature)	c.1703C>T. (p.Ala568Val)	(+) (affected father)	Letrozole (1.25 mg/day), spironolactone (20 mg tid), triptorelin from 4.7 years of age (6.9 years)	Decreased growth velocity, frequency of penis erection decreased
2	Gurnurkar et al.[8] (2021) (USA)	6 Months	Pubic hair, rapid growth acceleration	BA 12–18 months, elevated serumtestosterone (550 ng/dL), prepubertal response to GnRH ST	No	c.1733A>C (p.Asp578Ala)	NA	Anastrozole (1 mg daily), bicalutamide (25 mg daily) (14 months)	Significant improvement in linear growth, skeletal maturation, final height prediction
3	Nabhan and Eugster[16] (2019) (USA)	2.10 Years	Pubic hair, growth acceleration, masturbatory behaviors	BA 5.5 years, elevated serum testosterone (242 ng/dL), prepubertal response to GnRH ST	No	p.Asp578Gly	NA	Anastrozole (1 mg daily), bicalutamide (50 mg daily) (10.25 years)	Decrease in growth velocity, arrested pubertal development
4	Özcabı et al.[11] (2015) (Turkey)	6 Months	Pubic hair, acne, penile enlargement, Linear growth acceleration, Increased aggressive behavior	BA 4 years, very high serum testosterone (1,010 ng/dL), pubertal response of GnRH ST at 3.8 years	No	c.830G>T (p.Ser277Ile)	(-)	Anastrozole (1 mg daily), bicalutamide (50 mg daily), cyproterone acetate (NA), ketoconazole (10 mg/kg/day) GnRH analog from 4.7 years of age (32 months)	Slowing pubertal progression and bone age
5	Özcabı et al.[11] (2015) (Turkey)	17 Months	Pubic hair, penile enlargement, Linear growth acceleration	BA 3.5 years, high serum testosterone (479.2 ng/dL), prepubertal response of GnRH ST	No	c.1118C>T (p.Ala373Val)	(+) (asymptomatic carrier mother)	Anastrozole (1 mg daily), bicalutamide (50 mg daily), ketoconazole (10 mg/kg/day) (18 months)	Slowing pubertal progression and bone age
6	Yoshizawa-Ogasawara et al.[14] (2014) (Japan)	3 Years	Accelerated growth rate, rapid penile enlargement	BA 9.2 years, high serum testosterone (289 ng/dL), prepubertal response of GnRH ST	NA	c.1715C>T (p. Ala572Val)	NA	Anastrozole (1 mg daily), spironolactone (150 mg daily) (6 years)	Successfully decelerated BA advancement, Prolonged pubertal period, improved adult height
7	Mitre and Lteif[10] (2009) (USA)	4 Years	Increased penile and testicular size, growth acceleration, pubic hair, aggressive behavior	BA 9–10 years, elevated serum testosterone (125 ng/dL), prepubertal response of GnRH ST	No	c.935A>G (p. Asp312Ser)	NA	Anastrozole (1 mg daily), bicalutamide (50 mg daily) (16 months)	Prepubertal pattern of linear growth, slowing of bone age, resolution of aggressiveness
8[a]	Eyssette-Guerreau et al.[15] (2008) (USA)	32 Months	Accelerated growth velocity, pubic hair, developed muscles, facial acne	BA 4.6 years, high serum testosterone (510 ng/dL), prepubertal response of GnRH ST	No	p.Thr577Ile	(+) (asymptomatic carrier mother)	Ketoconazole (150 mg/day), cyproterone acetate (50 mg/day) (4 years)	Decreased growth velocity, Improved acne and irritability
9[a]	Eyssette-Guerreau et al.[15] (2008) (USA)	30 Months	Acne, increase in penile length with erections	Advanced BA, high serum testosterone (140 ng/dL), prepubertal response of GnRH ST	Yes (affected brother; patient 8)	p.Thr577Ile	(+) (affected brother; asymptomatic carrier mother)	Cyproterone acetate (50 mg/day), anastrozole (1 mg daily) (3 years)	Decreased growth velocity, improved in acne, advance in BA remained stable

BA, bone age; GnRH ST, gonadotropin-releasing hormone stimulation test; tid, three times a day; PAH, predicted adult height; NA, not available.
[a]Patients 8 and 9 were brothers. [b]Patients 12 and 13 were brothers.

(*continued*)

Table 2. Summary of phenotypes and genotypes in patients with familial male-limited precocious puberty in recent case reports (continued)

No.	Study	Age of onset	Symptoms at presentation	Clinical and laboratory findings	Family history	Mutation in the *LHCGR* gene	Family member with mutation	Treatment (dose) (duration of treatment)	Outcome
10	Kreher et al.[9] (2006) (Israel)	6.6 Years	Pubic hair, increase of testicular volume, rapid linear growth	BA 8.5 years, high serum testosterone (233 ng/dL), prepubertal response of GnRH ST	No	p.Ala572Val	NA	Bicalutamide (50 mg daily), anastrozole (1 mg daily) (44 months)	Decrease in growth velocity and skeletal maturation, Increase in PAH, decrease in pubic hair
11	Kreher et al.[9] (2006) (USA)	4.1 Years	Facial acne, pubic hair Increased penile length and testicular volume	BA 4.5–5 years, elevated basal LH level, High serum testosterone (432 ng/dL)	Yes(paternal great-grandfather, father, paternal uncle, 2 male cousins' short stature and precocious puberty)	p.Ile542Leu	(+) (affected father)	Bicalutamide (50 mg daily), anastrozole (1 mg daily), GnRH agonist from 3.4 years of age (leuprolide IM 7.5mg/mo) (17 months)	Decrease in growth velocity and skeletal maturation, Increase in PAH
12[b]	Latronico et al.[13] (2000) (Brazil)	3.5 Years	Increased penile length and testicular volume, pubic hair	BA 6 years, elevated serum testosterone (193 ng/dL), prepubertal response of GnRH ST	No	c.1103T>C. (p.Leu368Pro)	(+) (asymptomatic carrier mother)	NA	NA
13[b]	Latronico et al.[13] (2000) (Brazil)	2.5 Years	Increased penile length and testicular volume, pubic hair	BA 4 years, elevated serum testosterone (240ng/dL), prepubertal response of GnRH ST	Yes (affected brother; patient 12)	c.1103T>C. (p.Leu368Pro)	(+) (affected brother; asymptomatic carrier mother)	NA	NA
14	Latronico et al.[13] (2000) (Brazil)	4 Years	Frequent erections, Penile growth, enlargement of both testis, pubic hair	BA 13.6 years, elevated serum testosterone (265 ng/dL), pubertal response to GnRH ST at 7.11 years	Yes (father's short stature)	c.1703C>T. (p.Ala568Val)	NA	Cyproterone acetate (NA), GnRH agonist (leuprolide, 3.75 mg/mo)	NA
15	Present (Korea)	12 Months	Premature pubic hair, acne, accelerated linear growth	BA 4 years, highly elevated serum testosterone (574 ng/dL), prepubertal response of GnRH ST	Yes (paternal grandfather, father's short stature, precocious puberty)	c.1730 C>T (p.Thr577Ileu)	(+) (affected father)	Anastrozole (1 mg/day), bicalutamide (25 mg daily)	Sufficient suppression in pubertal progression, decelerating rate of linear growth

BA, bone age; GnRH ST, gonadotropin-releasing hormone stimulation test; tid, three times a day; PAH, predicted adult height; NA, not available.
[a]Patients 8 and 9 were brothers. [b]Patients 12 and 13 were brothers.

Table 1. Laboratory findings at baseline and after combination therapy with an antiandrogen and third-generation aromatase inhibitor

Variable	Baseline	A month after treatment	2 Months after treatment	3 Months after treatment	6 Months after treatment	Normal range
Testosterone (ng/mL)	5.74	6.79	8.26	7.85	8.85	<0.05
Estradiol (pg/mL)	<5.0	-	-	-	-	15
DHEA-S (ug/dL)	19.1	-	-	-	-	5–57
Cortisol (ug/dL)	10.44	-	-	-	-	3–21
α–fetoprotein (ng/mL)	14.1	9.7	6.1	-	-	0–10
Basal LH (mIU/mL)	<0.07	<0.07	< 0.07	<0.07	<0.07	0.02–0.15
Basal FSH (mIU/mL)	0.56	0.56	0.57	1.10	0.62	0.38–1.11
AST (IU/L)	19	22	18	20	19	0–40
ALT (IU/L)	11	14	11	13	10	0–41
BUN (mg/dL)	10.2	11.0	13.7	8.9	12.1	5–20
Creatinine (mg/dL)	0.32	0.37	0.31	0.31	0.32	0.2–0.4

DHEA-S, dehydroepiandrosterone sulfate; LH, luteinizing hormone; FSH, follicle-stimulating hormone; AST, aspartate transaminase; ALT, alanine transferase; BUN, blood urea nitrogen.

height. In addition, ketoconazole showed serious side effects, including hepatotoxicity and adrenal suppression.[3,9] A therapeutic regimen that combines spironolactone (a weak antiandrogen) and testolactone (an aromatase inhibitor) with deslorelin (a long-acting GnRH analog) at the onset of central precocious puberty has been shown to normalize the growth rate and bone maturation and to improve predicted height in boys with FMPP.[19,20] Most recent studies have demonstrated that the combination of bicalutamide (an antiandrogen) and anastrozole (a third-generation aromatase inhibitor) has shown better height outcomes than previous reports.[4,9,10] This combination treatment showed better potential for the preservation of final adult height than treatment with either agent alone.[5] Our patient also received this combination treatment and showed an impressive clinical response in pubertal progression, growth velocity, and skeletal maturation without any side effects.

Treatment regimens have evolved over the years, but there is no consensus regarding optimal treatment. Testosterone is not a good indicator for treatment efficacy, and clinical and auxological parameters are more important. Long-term follow-up that focuses on the auxological parameters rather than biochemical profiles is required. In our patient, treatment efficacy was monitored by physical examination and bone age progression. Bicalutamide and anastrozole may interfere with normal sex steroid profiles. However, information on the long-term effects on testicular function, lipid profiles, and bone mineral accrual of this therapeutic combination is limited, and further research is required.[9]

In conclusion, we described a case of FMPP in a Korean boy that was confirmed by identifying an *LHCGR* gene mutation. FMPP appears to be exceptionally rare or underrecognized in the Korean population. It should be considered in the differential diagnosis of peripheral precocious puberty, particularly when the family history of precocious puberty is limited to male family members.

Notes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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