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ORIGINAL ARTICLE

# Familial male-limited precocious puberty in neurofibromatosis type I

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**Abstract**
Precocious puberty in patients with neurofibromatosis type 1 (NF-1) is predominantly central in origin, with intracranial pathologies like optic glioma. We describe one patient with NF-1 who presented with precocious puberty with the eventual diagnosis of familial male-limited precocious puberty and share the potential pitfalls. He presented at 7 years of age with growth spurt and pubertal genitalia development with enlarged testicular volume of 7 mL, but LHRH stimulation test revealed blunted luteinizing hormone and follicle-stimulating hormone peak suggestive of a peripheral cause, contrary to the expectation due to the background of NF-1. Testosterone level was elevated with bone age advancement by 2 years. Genetic analysis revealed a previously reported heterozygous missense mutation of the luteinizing hormone/choriogonadotropin receptor gene Ala572Val. His father was also heterozygous for the same mutation but was apparently asymptomatic and not short. *Conclusion*: Our report illustrates two potential pitfalls in the clinical evaluation of patients with familial male-limited precocious puberty (FMPP). Firstly, patients with FMPP will have mild to moderately enlarged testes and should not be wrongly diagnosed as central precocious puberty without the gonadotropin-releasing hormone stimulation test. Secondly, family members with the same mutation may have different phenotypic severities, where some male carriers may have subtle features.

**Keywords** Familial male-limited precocious puberty · Testotoxicosis

**Abbreviations**

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| NF-1 | Neurofibromatosis type 1 |
| FMPP | Familial male-limited precocious puberty |
| LH | Luteinizing hormone |
| FSH | Follicle-stimulating hormone |
| LHRH | Luteinizing hormone-releasing hormone |
| GnRH | Gonadotropin-releasing hormone |

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## Background

Neurofibromatosis type 1 (NF-1) (OMIM 162200) is an autosomal dominant genetic disorder with an incidence of approximately 1 in 3,000 individuals [1], whereas familial male-limited precocious puberty (FMPP) (OMIM 176410) is an autosomal dominant genetic disorder with a prevalence of 1–9/1,000,000 (www.orpha.net). Although both conditions are rare and seemingly unrelated, and precocious puberty in patients with NF-1 is predominantly central in origin, associated with intracranial pathologies like optic glioma, we describe one patient with NF-1 who presented with precocious

puberty with the eventual diagnosis of FMPP and share the pitfalls we experienced.

## Clinical presentation

Patient A is a Chinese boy and the second child of non-consanguineous parents. He was diagnosed with NF-1 with multiple café au lait skin lesions, and magnetic resonance imaging (MRI) of the brain at the age of 2 years showed a left cerebral peduncle hamartoma. Ophthalmology review showed nodules on the iris suspicious of Lisch nodules. The diagnosis was made based on clinical criteria, and mutational analysis for NF-1 was not performed. He also had bilateral severe to profound sensorineural hearing loss with hearing aids. Screening also revealed that he had left hypoplastic kidney with grade I vesicoureteric reflux, but normal renal function. He was first referred at 7 years of age by his primary physician for the assessment of precocious puberty. His mother noticed that his penile length had increased 6 months prior to presentation, and there was a growth spurt 2 years prior with a height velocity of 9 cm per year. His 12-year-old brother, father, or other family members in the paternal side had no apparent history of precocious puberty. On examination, his testes were 7 mL (right) and 6 mL (left) (assessed with an orchidometer). He had Tanner stage 1 pubic hair with a penile length of 9 cm. In view of his background of NF-1 and testicular enlargement, the provisional diagnosis was central precocious puberty which is commonly associated with the development of optic glioma in NF-1 or due to more sinister tumor development, especially in the region of the hypothalamus or hydrocephalus [3, 11].

However, the gonadotropin-releasing hormone (GnRH) stimulation test which showed blunted peak luteinizing hormone (LH) level of 1.4 IU/L (normal basal range, 0.2–1.4 IU/L) and follicle-stimulating hormone (FSH) level of 1.8 IU/L (normal basal range, 0.1–3.8 IU/L) was consistent with peripheral precocious puberty. LH and FSH levels were taken at baseline and at 30, 60, and 90 min after the administration of intravenous LHRH 100 mcg. The testosterone level taken at 0 min was elevated at 6.41 nmol/L (normal prepubertal range, 0.1–1.2 nmol/L). His bone age (according to Greulich and Pyle atlas) was advanced at 9 years at a chronological age of 7 years [2]. The 17-hydroxyprogesterone was not clinically significant at 1.89 nmol/L (normal range, 0–1.4 nmol/L). Dehydroepiandrosterone sulfate level was normal at 0.61 nmol/L (normal range, 0.3–2 nmol/L). The beta-human chorionic gonadotropin (β-hCG) level was not elevated (<2 IU/L). MRI of the brain performed as part of his routine scheduled surveillance did not reveal any optic glioma or new brain lesion. Ultrasound of both testes did not reveal any mass lesion. Bone scan showed no evidence of fibrous dysplasia which would suggest McCune–Albright syndrome.

## Genetic analysis

FMPP was suspected, and direct sequencing of the LH/choriogonadotropin receptor (*LHCGR*) gene was performed using genomic DNA extracted from the peripheral blood (Gentra® Puregene® Blood Kit; QIAGEN, GmbH). Polymerase chain reaction (PCR) was performed using primers (a) 5′-CCTTTTGTTTCTTTGCCTTTA -3′ and (b) 5′-TGCCTAATGTACCTAAAA ATAAATAAT -3′, to amplify the amino acid-coding region of exon 11, of the *LHCGR* gene, the hotspot for constitutive activating point mutations. Each PCR reaction mixture of 25 μL contained 200 μM of each dNTP (Promega, Madison), 0.4 μM of each primer, 0.5 units of Taq polymerase in 10× PCR buffer (QIAGEN, GmbH), and 100 ng of the extracted genomic DNA. The PCR cycling conditions were as follows: initial denaturation step at 95 °C for 3 min, with 30 cycles of 45 s at 95 °C and 45 s at 55 °C, and for 1 min, 30 s at 72 °C, with a final extension step of 5 min at 72 °C. The amplicons were subjected to automated sequencing using the ABI Prism Big Dye Terminator Ready Reaction Kit (Perkin-Elmer, Foster City, CA, USA) and ABI Prism 3100 Genetic Analyser. Sequencing was performed using the primers described earlier. Whenever a sequence variant was found, both PCR and repeat forward and reverse sequencing were repeated. We found a heterozygous missense mutation of the *LHCGR* gene Ala572Val in patient A (Fig. 1). This mutation was previously reported to be pathogenic for FMPP and supported by in vitro functional studies, where the mutant LH receptor showed constitutively high basal of cAMP levels, but with normal agonist-induced cAMP response [12]. Family screening showed that his father was also heterozygous for the mutation, but not his mother and brother. However, his father was not short, with height of 170 cm (50th centile on the local male growth chart), and he did not recall having early puberty or behavioral issues when young.

The patient was offered a combination of spironolactone and anastrozole (as testolactone was not available), but the parents eventually opted for cyproterone acetate 70 mg/m$^2$ (25 mg OM, 50 mg ON) due to the high cost of anastrozole. He responded well with less frequent penile erections and less inappropriate sexual behavior. His subsequent bone age was assessed to be 11 years at a chronological age of 8 years and 3 months.

## Discussion

FMPP is uncommon, and the diagnosis may be difficult to establish initially. Contrary to the principle that increased testicular volume beyond 4 mL indicates that the precocious puberty is central in origin [10], patient A who was confirmed to have pseudoprecocious puberty from FMPP had testicular volumes up to 7 mL at presentation, a feature which is not uncommon in

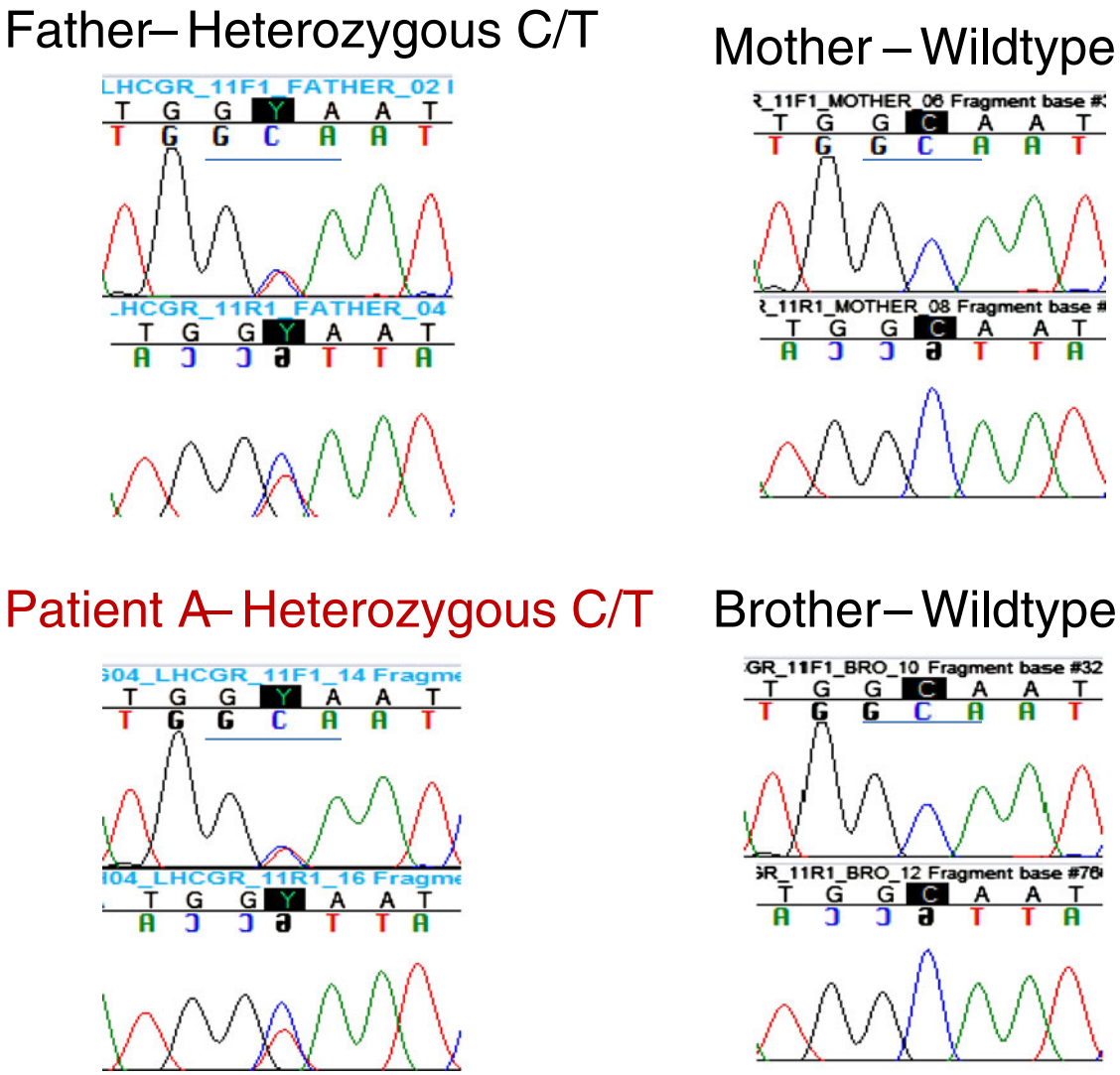


**Fig. 1** The patient's and his father's missense mutation in the *LHCGR* gene c.1715C>T leads to p.Ala572Val in contrast to his mother and brother

this condition. The key to the diagnosis was in the GnRH stimulation test in which the prepubertal peaks of LH and FSH prompted further investigations for the etiology of pseudoprecocious puberty. Assuming that with enlarged testicular volume in a patient with NF-1 indicates central precocious puberty is erroneous and could pose as a red herring.

Patient A's phenotype appeared relatively mild, as he presented slightly later at 7 years old, and his bone age was only advanced by 2 years. He was 133.2 cm (>97th centile) at presentation, and his predicted final height based on Bayley–Pinneau table was 176 cm (75th centile). His father was also found to be heterozygous for the mutation A572V, but he was apparently asymptomatic. It is observed in the other family pedigrees that the phenotype can be variable with poor phenotype–genotype correlation, and some male carriers may have subtle features and may not have short stature. It is possible that the father had a mild phenotype, and his early pubertal features might have gone unnoticed or perceived as a normal development by the father's parents and the father himself [5, 7, 9].

If patients with FMPP presented late and had entered true puberty, the diagnosis may elude the clinician. These patients might present for evaluation of tall stature and were found to have advanced bone age and pubertal stage for chronological age. There may also be history of pubic hair development, semen emission, or frequent erections before 9 years of age. A high index of suspicion is required, and genetic testing will be the only way to clinch the diagnosis.

Various treatment modalities have been described for FMPP. The use of oral cyproterone acetate 70–130 mg/m$^2$ daily was reported with decreased growth velocity and lowering of testosterone levels [4]. Spironolactone is an antiandrogen that antagonizes androgen at the receptor level, and testolactone is an aromatase inhibitor that blocks the conversion of androgen to estrogen. The combination of spironolactone (5.7 mg/kg/day; up to 450–500 mg per day)

and testolactone (40 mg/kg/day) has been used successfully [6, 8]. As testolactone is not available in many countries, it may be substituted with others such as anastrozole (off-label use). GnRH analogues may need to be initiated later as true central precocious puberty frequently starts when peripheral precocious puberty is blocked which can further compromise final adult height.

Our report illustrates a boy with two rare and seemingly unrelated genetic disorders. FMPP was diagnosed as the cause of the gonadotropin-independent precocious puberty after ruling out McCune–Albright syndrome and β-hCG-producing tumor. We identified two potential pitfalls in the clinical evaluation of patients with FMPP. Firstly, patients with FMPP will have mild to moderately enlarged testes and should not be wrongly diagnosed as central precocious puberty without the GnRH stimulation test. Secondly, family members with the same mutation may have different phenotypes.

**Conflict of interest** The authors declare that they have no conflict of interest.

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