Familial Male-Limited Precocious Puberty (FMPP) and Testicular Germ Cell Tumors

Case series and overview of the literature

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Disclosure statement: The authors have nothing to disclose.

Keywords (>3): Testotoxicosis, familial male limited precocious puberty, activating luteinizing hormone receptor, testicular tumors, germ cell tumors, peripheral precocious puberty
Abstract

Objective: The purpose of this study is to report development of a malignant testicular germ cell tumor (GCT) in two young adult males with Familial Male-limited Precocious Puberty (FMPP) due to (LHCGR) pathogenic variants in two families. Secondary, to study the possible relation between FMPP and testicular tumors and to investigate whether FMPP might predispose to development of malignant testicular tumors in adulthood a literature review is conducted.

Methods: Data on six cases in two families are obtained from the available medical records. In addition, a database search is performed in Cochrane, Pubmed and Embase for studies that report on a possible link between FMPP and testicular tumors. Results: The characteristics of six males with FMPP based on activating luteinizing hormone receptor (LHCGR) germline pathogenic variants are described, as well as details of the testicular GCTs. Furthermore, literature review identified four more patients with signs of FMPP and a (precursor of a) testicular GCT in adolescence or adulthood (age 15 to 35 years). Additionally, twelve patients with signs of precocious puberty and, simultaneously, occurrence of a Leydig cell adenoma or Leydig cell hyperplasia are reported. Conclusion: There is a strong suggestion that FMPP might increase the risk of development of testicular GCTs in early adulthood compared to the risk in the general population. Therefore, prolonged patient monitoring from mid-pubertal age onwards including instruction for self-examination and periodic testicular ultrasound investigation in patients with a germline LHCGR pathogenic variants might contribute to early detection and thus early treatment of testicular GCT.

Introduction

Familial male-limited precocious puberty (FMPP), also referred to as testotoxicosis, is characterized by LH-independent precocious puberty. This disease is caused by an autosomal dominant inherited activating germline pathogenic variants of the gene coding for the luteinizing hormone/choriogonadotropin receptor (LHCGR), which belongs to the G-protein coupled
receptor 1 family. In males, activating pathogenic variants of the LHCGR gene cause excessive production of testosterone which triggers early peripheral (precocious) puberty, while the overactive receptor does not cause clinically relevant symptoms in girls.\textsuperscript{2,3} Activating pathogenic variants of the LHCGR gene have been identified and described since 1993.\textsuperscript{1,4} Pathogenic variants in the sixth transmembrane segment (TM6) and the third intracellular loop of the G protein-coupled receptor are described as the hot spot of amino acid alterations, however changes in other transmembrane segments also have been reported.\textsuperscript{5} Kremer \textit{et al.} have reported a total of 12 LHCGR gene pathogenic variants in 68 independent patients and families, and their findings suggested that only pathogenic variants of specific amino acids are responsible for constitutive activation which can also transmitted to consecutive generations.\textsuperscript{2}

Normally, at puberty the LHCGR mediates action of LH on the testosterone synthesis by Leydig cells. As a result of the activated LHCGR status in FMPP, Leydig cell hyperplasia occurs at a young age.\textsuperscript{6} Boys, typically between 2 and 6 years of age, present with precocious pubertal development, growth of the penis and enlargement of the scrotum and testes, as well as linear growth acceleration, progressive bone age advancement, growth of pubic and facial hair.\textsuperscript{2,7} Consequently, this eventually may lead to compromised adult height as well as psychological effects associated with precocious puberty. Final height modestly below sex-adjusted midparental height and within the range for adult males in the general population has been reported.\textsuperscript{8} Current treatment consists of a combination therapy of a potent nonsteroidal anti-androgen agent (bicalutamide) and a third-generation aromatase inhibitor.\textsuperscript{9,10} This combination treatment appears to be a safe and effective approach while only minor adverse events have been described. However, data on long-term outcome of final height and fertility remains scarce; therefore, close follow-up of these patients remains important.\textsuperscript{7}

In this study, we report two families with FMPP. All affected males have a pathogenic variant in the LHCGR gene; c.1624A>C p.(Ile542Leu). This specific variant has previously been described to be pathogenic in three familial cases and one sporadic case.\textsuperscript{11} Because two out of three
fathers developed a malignant testicular GCT in young adulthood, we wondered whether this
testicular(GCT) in young adulthood, we wondered whether this
might be related to the FMPP and if follow-up in FMPP patients after puberty is necessary for
early detection of these tumors. In order to investigate whether FMPP might predispose to
development of malignant testicular GCTs in adulthood, we conducted a literature search.

Methods

Case series
In this study three father and son couples in two families with FMPP are described, of whom two
fathers were diagnosed with a malignant testicular GCT in young adulthood. In both families the
c.1624A>C p.(Ile542Leu) pathogenic variant in the LHCGR gene was found. Data on all six
cases were obtained from the available medical records. Pathology reports and specimens of
both tumors were revised by an expert pathologist (R.R.K.). The study was approved by the
institution review board of the UMCU and informed consent was obtained from all affected
individuals.

Genetic analysis
Genomic DNA was extracted from EDTA blood of each patient by standard methods. The coding
region and exon–intron boundaries of the LHCGR gene (GenBank: NM_000233) were amplified
from genomic DNA. Sanger sequencing was performed using the BigDye Terminator
Sequencing Kit (Thermo Scientific) and ABI 3730 XL (Applied Biosystems). Coding sequences
and flanking intron sequences were analyzed with SequencePilot (SeqPatient, JSI Medical
Systems GmbH, Ettenheim, Germany). PCR and sequencing primers are available on request.

Literature review
Review of the literature was based on a search for all available published articles in the
databases Cochrane, Pubmed and Embase. The databases were searched until November
2020 for published studies that report or describe a possible link between FMPP and testicular
tumors. The checklist of the PRISMA Statement was used to systematically search and include
literature. However, due to the scarcity of literature describing both conditions, not all
requirements of the checklist could be met. The search terms and their synonyms are listed in
Supplementary Table 1. After exclusion of duplicates, the remaining studies were screened for
title and abstract by two authors (C.K. and A.M.) independently. The full texts of the articles that,
after consensus, were labeled as potentially eligible were then assessed and included in the
review. Subsequently, the information/data described in the included articles was manually
searched according to the Guidelines for Snowballing in Systematic Literature.

To determine the level of evidence of the included articles, we used the Levels of Evidence
(2011) of the Oxford Centre for Evidence Based Medicine.

Results

Case series

The clinical characteristics of the three boys (V-1 and V-3 of Family A; II-1 of Family B) and their
fathers (IV-3 and IV-10 of Family A; I-1 of Family B) are summarized in Table 1.

Family A

At the age of 27 years, individual IV-10 was diagnosed with a malignant testicular GCT on the
left side. He had presented at the age of 5 years with signs of precocious puberty and a positive
family history for FMPP, as depicted in Figure 1. Until the age of 12, he was treated with
ketoconazole and progression of puberty was monitored thereafter. Radical orchidectomy
followed presentation with a testicular mass. Histopathology revealed an embryonal carcinoma
(being a type of non-seminoma) limited to the testis (alpha fetoprotein (AFP) and beta human
chorionic gonadotropin (bHCG) negative), and germ cell neoplasia in situ (GCNIS). A few
months after the initial orchidectomy, a recurrence of the non-seminoma with tumor positive
para-aortic lymph nodes was diagnosed. After chemotherapy with bleomycin, etoposide and 
platinum (BEP), individual IV-10 remained in complete remission. There was no family history of 
testicular tumors.

As far as other family members in this large family tree are concerned, we do not have 
information on possible precocious puberty or genetic analysis.

The son of IV-10, V-3, presented at the age of four years with suspected FMPP based on growth 
of facial and pubic hair, aggressive behavior, and an increased growth rate. At physical 
examination, testicular volume was eight ml on both sides, which in the Dutch population usually 
matches pubertal development in boys aged 12-15. Serum testosterone was markedly elevated 
(16.1 nmol/l, normal value at age four <0.5 nmol/l); with low LH and FSH (both <0.1 IU/l).

In the same Family A, but not closely related (Figure 1), IV-3 also presented at the age of six 
years with signs of precocious puberty. He was clinically diagnosed with FMPP and he received 
treatment with multiple (combinations of) therapies up to the normal age of pubertal onset. 
During follow-up thereafter and confirmed by recent testicular ultrasound, no testicular 
abnormalities have developed.

V-1, the son of IV-3, also presented with pubic hair development and linear growth acceleration 
at the age of four years. During physical examination his testes had an estimated volume of 6-8 
ml. Elevated serum testosterone (7.7 nmol/l) and low LH and FSH (both <1.0 IU/l) were found. 
No scrotal ultrasound was performed at presentation. The increased testicular volume can be 
related to the effect of the LH receptor activation, this patient underwent an LHRH test at first 
presentation which did not show central precocious puberty.

DNA-analysis in peripheral blood of both V-3 and V-1, performed after initial presentation with 
precocious puberty, confirmed a heterozygous pathogenic variant at c.1624A>C p.(Ile542Leu) in 
the LHCGR gene in both cases, in line with the clinical diagnosis of FMPP.
Family B

At the age of 25, patient I-1 presented with a suspicious scrotal mass in his right testicle; ultrasound revealed a hypo-echoic solid mass and radical orchidectomy was performed. The family history for testicular tumors was negative. Histological evaluation reported an embryonal carcinoma (non-seminoma) with angio-invasion (AFP and bHCG negative) (Figure 2). The testicular parenchyma did not show Leydig cell hyperplasia. He was treated with adjuvant chemotherapy as lymph node involvement was found, and he has remained in complete remission since. The medical history of this man had also started with signs of precocious puberty at the age of only two years, similar to males (fathers) of Family A. Years of extensive diagnostic investigation followed, and he was treated with cyproterone acetate up to puberty. When genetic testing became available in the 1990’s, DNA analysis confirmed FMPP based on a LHCGR pathogenic variant.

II-1, the son of I-1, presented at age three with testicular enlargement, growth of pubic hair, acne, and accelerated growth. His testes had an estimated volume of 6 ml (normally < 4 ml at this age). Serum testosterone was highly elevated (15 nmol/l, normal <0.5 nmol/l), and gonadotrophins were low (LH 0.87 IU/l; FSH <0.50 IU/l). Scrotal ultrasound showed no evidence of a testicular tumor. Suspicion of FMPP was confirmed by the presence of the same pathogenic variant in the LHCGR gene as was found in Family A. The family tree of Family B is presented in Figure 3.
Pregnancies of V-3, V-1 and II-1 were all achieved without the help of assisted reproductive technologies. The option of genetic counseling either before or during pregnancy or after birth as well as the option of genetic testing in male offspring had not been brought to attention to the affected fathers.

**Genetic result**

DNA sequencing analysis of the LHCGR gene showed a heterozygous missense variant c.1624A>C p.(Ile542Leu) in all members with FMPP in Family A (IV-3, V-1, IV-10, V-3). The same variant in the LHCGR gene was also detected in males with FMPP in Family B (I-1 and II-1). The missense variant p.Ile542Leu is located in the fifth transmembrane helix and has been reported previously to be an activating pathogenic variant in three familial cases and one sporadic FMPP case.\(^1\) This variant is not present in the Genome Aggregation Database (gnomAD v2.1.1, https://gnomad.broadinstitute.org).\(^2\) This variant can be considered to be pathogenic according to ACMG guidelines (PS3 PS4 PM1 PM2 PP1 PP4).\(^3\) Further genetic testing in both affected families has been a matter of attention but lies without the scope of this report.

**Literature review**

**Literature search**

The literature search in Cochrane, Pubmed and Embase provided a total of 65 studies that report or describe a possible link between FMPP and testicular tumors, of which twenty-two articles were duplicates. Thirty-five of the 43 remaining articles were excluded based on title and abstract screening. Of the eight potentially eligible studies, two only consisted of an abstract and one did not match the focus of this study, one further study consisted of an overview of the literature. Manual searching lead to inclusion of three more studies, providing a total of eight included full text articles. Figure 4 gives an overview of the search process.
Characteristics of the included studies

Table 2 and 3 show the (clinical) characteristics of the eight included studies. Five studies describe a single case\textsuperscript{18–22} and three reports include two or more patients\textsuperscript{6,23,24}, resulting in a total of sixteen patients.

Table 2 summarizes four case reports that describe patients with FMPP who later in adolescence or adulthood developed a testicular (germ cell) tumor (age at FMPP presentation: range 10 months to eight years; age at diagnosis of testicular tumor: range 15 to 35 years).\textsuperscript{18,20–22} Three patients were diagnosed with a malignant testicular GCT (including an embryonal carcinoma, a seminoma and a mixed GCT)\textsuperscript{18,20,22}. The fourth patient with a Leydig cell adenoma and GCNIS, the latter being the precursor lesion for all malignant testicular GCTs, both seminoma and non-seminoma\textsuperscript{21}. An \textit{LHCGR} pathogenic variant had been identified in three of the four patients in whom DNA analysis had been performed.

On the other hand, Table 3 summarizes four studies that report on in total twelve patients who presented simultaneously with peripheral precocious puberty and (suspicion of) an unilateral testicular mass or testicular asymmetry on ultrasound (median age: 6 years, range 2 to 8 years).\textsuperscript{6,19,23,24} Eleven of these 12 patients have been treated with an orchidectomy, except for one boy who underwent testis sparing surgery. The majority (10) of the tumors appeared to be Leydig cell adenomas\textsuperscript{6,23,24}, two were classified as nodular Leydig cell hyperplasia.\textsuperscript{6,19} Ten boys showed a somatic \textit{LHCGR} gene pathogenic variant in the removed testicular tissue without a germline pathogenic variant. Furthermore, in two boys \textit{LHCGR} pathogenic variants were identified in both peripheral blood as well as the removed testicular tissue; examination of the testicular tissue in these two boys showed nodular Leydig cell hyperplasia in one boy and a Leydig cell adenoma in the other boy.
Discussion

This study reports on two males with FMPP who developed a testicular GCT and contains an analysis of the existing literature on the occurrence of testicular tumors in patients with FMPP, with the aim to analyze whether FMPP might predispose to development of malignant testicular tumors in adulthood.

Firstly, the observation in our clinic that in two families men with FMPP had developed a testicular tumor in adulthood raised the question whether their sons, and boys with FMPP in general, are at an increased risk for development of testicular malignancies. Literature research revealed four additional cases of men with FMPP that developed (the precursor of) a testicular malignancy.

The prevalence of both FMPP and, to a slightly lesser extent, malignant testicular GCT is rare. Making the simultaneous occurrence of these conditions remarkable. The incidence of a testicular carcinoma is approximately 6/100,000 men per year, with a small annual increase for no clearly documented reason, and mortality is 0.3/100,000 men per year. Furthermore, prevalence of testicular tumors is most common in adolescents, compromising 12% of cancers in the 15-19 years age range.

The co-occurrence of FMPP and a testicular malignancy in adulthood in at least six cases is remarkable and might indeed suggest an increased risk for development of malignant testicular tumors in males with FMPP. Quantification in patients with FMPP of the risk for development of a testicular malignancy later in life is not possible due to the small number of FMPP patients, with an estimated prevalence of <1/1,000,000. Of note, predisposition does not appear to be tied to one pathogenic variant, as the pathogenic variant described in both families in this report is different from those reported for the cases in literature (Table 3). However, all are germline activating pathogenic variants within exon 11 of the LHCGR gene.
Both benign adenomas such as we report in Table 3 as well as malignant tumors have also been reported for other diseases with activating receptor pathogenic variants. For example, in McCune Albright Syndrome (MAS), which is caused by activating pathogenic variants in G-protein coupled receptors, testicular tumors, predominantly Leydig cell tumors (LCT) and Sertoli cell tumors (SCT) have been repeatedly described. Moreover, Boyce et al. also suspect MAS to be a predisposing factor for testicular malignancy after description of a patient with MAS who had both an embryonal carcinoma and a seminoma without predisposing exposures or a positive family history.\textsuperscript{29} This analogy in occurrence of testicular abnormalities in individuals with an activating G-protein coupled receptor mutation could support the hypothesis that activating \textit{LHCGR} pathogenic variants may well increase the risk of development of a testicular GCT.

Secondly, the question was raised whether an increased malignancy risk also exists for testicular tumors identified in boys who present with asymmetrical testicular enlargement or testicular mass and simultaneous signs of peripheral precocious puberty. Interestingly, in all boys reported in Table 3, testicular histology was found to be benign in nature. Of note, it is unknown how these lesions might develop when left untreated; as in one of the cases reported in literature actually showed seminoma in an adult male at age 35 while testicular biopsy early in childhood had shown interstitial cell hyperplasia.\textsuperscript{22} Of note, an additional article has been published after we performed the systematic search of the literature. The authors report two additional patients who presented with simultaneous signs of precocious puberty and a testicular mass, while pathology assessment revealed a benign LCT in one boy and a malignant LCT in the other. Genetic analysis on the \textit{LHCGR} gene or other genes was not reported for these two cases.\textsuperscript{30} We need to point out that one of these two additional cases had a malignant testicular lesion in contrast to all previous patients reported and summarized here, who all had benign lesions.
Recent literature offers hypotheses that might explain the suggested increased risk for development of testicular malignancies in males with a germline pathogenic variant of the \textit{LHCGR} gene. Abnormally increased testosterone levels, assumed to be present since fetal development, are thought to cause an imbalance in steroidogenesis and accelerated puberty, which might lead to disturbed gonocyte differentiation and promotion of neoplastic changes. However, no clear evidence of the underlying mechanism has yet been provided. \textsuperscript{18,21,22} Gonadal stromal cells during early development express both transcription factor \textit{Sex-determining Region Y} (SRY) as well as its target gene SOX9, in the presence of a Y-chromosome. This leads to formation of Sertoli cells, which create a specific microenvironment that allows the differentiation of gonocytes into spermatogonia. \textsuperscript{31} SRY gene pathogenic variants are present in 10-15\% of the 46XY disorders of sex development (DSD) patients. These patients have an increased risk of development of a malignant gonadal GCT, which is related to prolonged existence of the embryonic phenotype of the germ cells, exemplified by the continuous expression of OCT3/4. One of the suggested candidate genes located within the so-called GonadoBlastoma on the Y-chromosome (GBY) region is Testis Specific Protein on the Y-chromosome (TSPY). This is suggested to be explained by its survival and proliferation inducing effect on embryonic germ cells. \textsuperscript{32-34} A similar mechanism, although now indirect due the effect of the pathogenic variant in the supporting cell compartment (i.e., Leydig cell), might inhibit the maturation process of the gonocyte towards spermatogonia, and as such result in an increased risk of development of testicular GCTs in case of a \textit{LHCGR} germline pathogenic variant.

This study does have some limitations. Firstly, as FMPP does not occur frequently, numbers are very low and there is a fair amount of uncertainty around the magnitude of the increased risk of testicular malignancies in these patients. Additionally, the current literature only consists of case reports. There also remains uncertainty about the pathophysiology of tumor development in both patients with a germline as well as a somatic pathogenic variant.
In view of the results described, we suggest increased awareness for the risk of development of testicular malignancy in patients with FMPP. Therefore, prolonged follow-up of these patients is advised during and after puberty, when the precocious puberty is no longer an issue and initial increased testosterone production does not require further follow-up or treatment as it had become age appropriate. Instruction of these patients to perform monthly scrotal (self-)examination and annual scrotal ultrasound might be justified from 12 to 40 years of age, to allow early detection of testicular malignancies. Therefore, we suggest a flowchart to assist clinicians in their considerations regarding follow-up in boys with symptoms of precocious puberty and a germline \textit{LHCGR} pathogenic variants (Figure 5).

In conclusion, there is a suggestion that the likelihood of development of testicular malignancy in (early) adulthood is increased in patients with FMPP based on a germline pathogenic variant in the \textit{LHCGR} gene. Therefore, self-examination and ultrasound follow-up from 12 to 40 years of age might contribute to early detection and thus early treatment of testicular tumors.

\textbf{Funding}: This research received no external funding.

\textbf{Conflicts of interest}: The authors declare no conflict of interest.

\textbf{Data Availability Statement}: The dataset generated and analyzed during the current study is not publicly available but is available from the corresponding author on reasonable request.
References


doi:10.1210/jc.84.3.1136


doi:10.1210/jc.84.3.1136


doi:10.1515/jpem.2010.161


Legends for Figures and Tables

Figure 1: Family tree of Family A. Precocious male puberty and a germ line mutation in the luteinizing hormone/choriogonadotropin receptor (LHCGR) gene indicated in black; ● = obligate carrier.

Data on mutation analysis of the (LHCGR) gene was only available for the individuals who are underlined and depicted in bold numbers.

Figure 2: A. Hematoxylin and eosin staining of embryonal carcinoma of patient I-1, showing typical morphology with sheets of undifferentiated cells with atypical nuclei and prominent nucleoli. B. Immunohistochemistry with OCT3/4 showing strong nuclear staining of all tumor cells. C. Immunohistochemistry with CD30 showing characteristic membranous staining of tumor cells.

Figure 3: Family tree of Family B. Precocious male puberty and a germ line mutation in the luteinizing hormone/choriogonadotropin receptor (LHCGR) gene indicated in black.

Figure 4: Flowchart of included and excluded articles during the systematic literature search.

Figure 5: Flowchart depicting suggested follow-up in boys presenting with symptoms of precocious puberty and a germ line mutation in the luteinizing hormone/choriogonadotropin receptor (LHCGR) gene.

FMPP = Familial Male-Limited Precocious Puberty; FSE = Frozen section examination.

Table 1: Clinical characteristics of the two families with Familial Male-Limited Precocious Puberty (FMPP).

* = Age of onset FMPP in years; † = Age at diagnosis of testicular tumor; FMPP = Familial Male-Limited Precocious Puberty; GCT = Germ cell tumor; ‡ = Substitution of isoleucine for leucine at position 542; ‘’ = Family as depicted in Figure 1; ‘’’ = Family as depicted in Figure 3.

Table 2: Included articles that described patients with first peripheral precocious puberty and later in life, during adolescence or adulthood, development of a testicular tumor. * = Number of patients with a testicular tumor included in study; † = Level of evidence based on the Oxford Centre for Evidence-Based Medicine: Levels of Evidence (2011); ‡ = Age at diagnosis; FMPP = Familial Male-Limited Precocious Puberty; ‡ = Age at onset; GCNIS = Germ cell neoplasia in situ; NP = Not performed; PB = Peripheral blood; TT = Testicular tissue; hLHR = Human luteinizing hormone/CG receptor; LHCGR = Luteinizing hormone/choriogonadotropin receptor.

Table 3: Included articles that described patients with simultaneous presentation of peripheral precocious puberty and a testicular tumor. * = Number of patients with a testicular tumor included in study; † = Level of
evidence based on the Oxford Centre for Evidence-Based Medicine: Levels of Evidence (2011)\textsuperscript{15}; ** = Age at diagnosis; PB = Peripheral blood; TT = Testicular tissue; LHCG = Luteinizing hormon/choriogonadotropin receptor.

<table>
<thead>
<tr>
<th>Family</th>
<th>Age</th>
<th>Treatment</th>
<th>DNA</th>
<th>Age</th>
<th>Side</th>
<th>Histopathology</th>
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<td><strong>Father (A: IV-10)</strong></td>
<td>5</td>
<td>Ketoconazole</td>
<td>c.1624A&gt;C (p.Ile542Leu)\textsuperscript{#}</td>
<td>27</td>
<td>Left</td>
<td>Non-seminoma</td>
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<tr>
<td><strong>Patient (A: V-3)</strong></td>
<td>5</td>
<td>Letrozole + Bicalutamide</td>
<td>c.1624A&gt;C (p.Ile542Leu)\textsuperscript{#}</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>Father (A: IV-3)</strong></td>
<td>6</td>
<td>Ketoconazole; Spironolactone + Testolactone; Cyproterone acetate</td>
<td>c.1624A&gt;C (p.Ile542Leu)\textsuperscript{#}</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Letrozole + Bicalutamide</td>
<td>c.1624A&gt;C (p.Ile542Leu)\textsuperscript{#}</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td><strong>Family B</strong></td>
<td>2</td>
<td>Cyproterone acetate</td>
<td>c.1624A&gt;C (p.Ile542Leu)\textsuperscript{#}</td>
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<td>Right</td>
<td>Non-seminoma</td>
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<td><strong>Father (B: II-1)</strong></td>
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<td>Letrozole + Bicalutamide</td>
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<td>Study</td>
<td>Oxford level</td>
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<td>Age**</td>
<td>Symptoms at presentation</td>
<td>Suspicion testicular tumor</td>
<td>Treatment</td>
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<td>Mortensen 2017 (18)</td>
<td>4</td>
<td>1</td>
<td>10 months</td>
<td>Pubic hair, grow of genitals, hands and feet</td>
<td>No; bilateral testicular biopsies (age 1.5 years) showed Leydig cell hyperplasia</td>
<td>Ketoconazole c.1732G&gt;T p.(Asp578Tyr) (PB) (de novo)</td>
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<td>Senniappan 2014 (15)</td>
<td>4</td>
<td>1</td>
<td>Before the age of 8 years</td>
<td>Pubic and facial hair, growth spurt, pubertal staging G4P4A2</td>
<td>No; testicular ultrasound revealed no evidence of tumor</td>
<td>Anastrozole, spironolactone</td>
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<tr>
<td>Winston 2014 (17)</td>
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<td>1</td>
<td>8 years</td>
<td>Tanner stage 4 genitalia, pubic hair, body odor, acne and linear growth acceleration</td>
<td>No; scrotal ultrasound showed normal, symmetrical testes</td>
<td>Anastrozole, bicalutamide</td>
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<tr>
<td>Martin 1998 (19)</td>
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<td>1</td>
<td>27 months</td>
<td>Enlargements of genitals, appearance of pubic hair</td>
<td>No; testicular biopsy showed interstitial cell hyperplasia and evidence of early spermatogenesis</td>
<td>Medroxyprogesterone acetate c.1733A&gt;G p.(Asp578Gly) (PB)</td>
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<td>Symptoms at presentation</td>
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<tr>
<td>Boot 2011 (6)</td>
<td>4</td>
<td>7</td>
<td>4 years</td>
<td>Linear growth acceleration, frequent erections</td>
<td>Yes; ultrasound of the testis showed a tumor in the right testis</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 years</td>
<td>Linear growth acceleration and early pubertal development</td>
<td>Yes; ultrasound showed an oval process in the right testis</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.5 years</td>
<td>Severe form of precocious puberty</td>
<td>Yes; ultrasound examination using high resolution showed small tumors in one testis</td>
<td>Spironolactone and testolactone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.5 years</td>
<td>Severe form of precocious puberty</td>
<td>Yes; ultrasound examination using high resolution showed small tumors in one testis</td>
<td>Spironolactone and testolactone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.5 years</td>
<td>Severe facial acne and pubarche</td>
<td>Yes; high resolution ultrasound examination showed a small tumor in the right testis</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.4 years</td>
<td>Precocious puberty (not specified)</td>
<td>Yes; ultrasound showed a tumor in the right testis</td>
<td>None</td>
</tr>
<tr>
<td>Canto 2002 (21)</td>
<td>4</td>
<td>2</td>
<td>4 years</td>
<td>Early pubertal development (not specified)</td>
<td>Yes; a discrete testicular mass was palpable and testicular ultrasound showed a unilateral left mass</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 years</td>
<td>Early pubertal</td>
<td>Yes; unilateral</td>
<td>None</td>
</tr>
<tr>
<td>Leschek 2001 (16)</td>
<td>4</td>
<td>1</td>
<td>4 years</td>
<td>Precocious puberty (not specified)</td>
<td>Ultrasound showed a unilateral mass right</td>
<td>Spironolactone, testolactone and deslorelin</td>
</tr>
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<tr>
<td>Liu 1999 (20)</td>
<td>4</td>
<td>3</td>
<td>8.3 years</td>
<td>Precocious puberty that had begun 1-2 years previously</td>
<td>Yes; unilateral mass on scrotal ultrasound</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>7.5 years</td>
<td>Precocious puberty that had begun 1-2 years previously</td>
<td>Yes; unilateral mass on scrotal ultrasound, mass also palpable</td>
<td>None</td>
<td>Testis sparing surgery right</td>
<td>Leydig cell adenoma</td>
</tr>
<tr>
<td></td>
<td>7.8 years</td>
<td>Precocious puberty that had begun 1-2 years previously</td>
<td>Yes; unilateral mass on scrotal ultrasound</td>
<td>None</td>
<td>Orchidectomy left</td>
<td>Leydig cell adenoma</td>
</tr>
</tbody>
</table>
30 studies in PubMed
35 studies in Embase
0 studies in Cochrane

65 studies in total

22 studies resolved after screening for duplicates
35 studies excluded by title and abstract

8 potentially relevant studies

Studies only consisting of an abstract (n = 2)
Studies that did not match research question (n = 1)

5 remaining studies

Backward and forward snowballing of references and citing articles of the remaining studies (n = 3)

8 studies included in the review
Boys with symptoms of precocious puberty AND A germ line mutation in the LHCGR gene (FMPP)

From 12 to 40 years of age:
Scrotal (self-) examination AND Annual scrotal ultrasound

In adulthood:
Refer to geneticist for counseling regarding heritability AND Family planning

No abnormalities

(Suspicion of) testicular tumor

Laboratory examination (AFP/bHCG) AND Consider additional imaging

In suspicion of malignancy: referral to urologist for testicular biopsy (FSE) and/or orchidectomy