STK11 gene variant (Peutz-Jeghers Syndrome) presenting with unilateral pre-pubertal gynaecomastia and macro-orchidism without muco-cutaneous pigmentation or gastrointestinal symptoms

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INTRODUCTION

We report two male siblings presenting with pre-pubertal gynaecomastia and macro-orchidism, who were later diagnosed with Peutz-Jeghers Syndrome (PJS) secondary to a *STK11* gene variant. Neither child fulfilled the clinical criteria for diagnosis at presentation, with no gastrointestinal symptoms, mucocutaneous pigmentation, nor known family history of PJS in a close relative[1].

Gynaecomastia is increasingly reported in PJS due to overexpression of testicular aromatase, which leads to the conversion of adrenally-derived androstenedione to estrone/ oestradiol in pre-pubertal boys, which also drives growth acceleration and skeletal maturation. A large-cell calcifying Sertoli cell tumour (LCCSCT) may also present with these features and given its association with PJS, is an important diagnosis to exclude

CASE REPORT

Table 1: Clinical features at presentation

Presentation	Sibling 1	Sibling 2
Age	3 years	3 years
Clinical features	Height 75th centile (TCR 25th – 98th centile) **Unilateral (right-sided) gynaecomastia (B2-3)** P1, G1, **TV 4mls** No mucocutaneous pigmentation	Height 91st centile (TCR 25th – 98th centile) **Bilateral gynaecomastia (B2-3)** P1, G1, **TV 4mls** No mucocutaneous pigmentation

Neither sibling reported any symptoms and were previously fit and well. Baseline investigations for Sibling 1 were normal (Table 2). Sibling 2 had an advanced bone age and evidence of testicular microcalcification on ultrasound, which was not thought to be indicative of widespread tumour.

Six-monthly clinical follow-up of both siblings did not identify acceleration in height velocity or progression of gynaecomastia or macro-orchidism. By 8 years Sibling 1's right-sided gynaecomastia had improved - only nipple prominence was evident.

Genetic investigations revealed a paternally-inherited heterozygous pathogenic variant **c.910C>T p.(Arg304Trp) in exon 7 of the *STK11* gene** in both siblings. Their father was asymptomatic and underwent a surveillance video capsule endoscopy, which identified multiple intestinal polyps throughout his small bowel, confirming a diagnosis of familial PJS.

Abbreviations TCR target centile range, TV testes volume; CA chronological age; BA bone age; MAS McCune Albright Syndrome CAH congenital adrenal hyperplasia; PAIS partial androgen insensitivity syndrome

Table 2: Investigation results

	Sibling 1	Sibling 2
FT4 (7.5 – 21.1 pmol/L)	12.5	12.6
TSH (0.7 – 8.5 mu/L)	1.75	2.33
FSH (0.4 – 1.6 iU/L)	<0.2	0.4
LH (<0.5 iU/L)	0.3	0.2
Oestradiol (<73 pmol/L)	<73	<73
Prolactin (55.4 – 276 mu/L)	121	162
Testosterone (0 – 0.5 nmol/L)	<0.4	<0.4
Androstenedione (0.1 – 0.6 nmol/L)	<0.2	0.4
DHEAS (<0.6 umol/L)	0.4	0.4
HCG	<0.5	<0.5
AFP (0 – 10 ku/L)	1.87	5.52
Genetic tests	Normal CGH array	46 XY
LHRH test LH 0, 30 & 60 mins FSH 0, 30 & 60 mins	 0.2 – 0.6 – 0.4 <0.2 – 0.5 – 0.6	 <0.2 – 0.3 – 0.3 <0.2 – 0.6 – 0.8
Urine steroid profile	Normal	Normal
Wrist x-ray	CA 3 years 9 months BA 3 years 6 months	**CA 4 years 1 month** **BA 6 years**
Testicular ultrasound	Not tolerated	**Bilateral testicular microlithiasis**

LEARNING POINTS

- **The 910C>T *STK11* gene variant is pathogenic for PJS and displays phenotypic variability.**
- **PJS may present without classical diagnostic features.**
- **PJS is a recognised cause of prepubertal gynaecomastia in children. Surveillance for signs of oestrogen excess is essential - aromatase inhibitors may be a future consideration.**
- **PJS is associated with LCCSCT, which may cause a bilateral increase in TVs. Annual screening via examination and ultrasound is important.**
- **Prepubertal macro-orchidism may occur in the absence of a LCCSCT and endocrinological evaluation must exclude peripheral and central precocious puberty.**

REFERENCES
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DISCUSSION

We are the first to report a paediatric diagnosis of PJS with pre-pubertal unilateral gynaecomastia and prepubertal macro-orchidism, without muco-cutaneous pigmentation or gastrointestinal symptoms.

Prepubertal unilateral gynaecomastia has not been reported in association with PJS and is an extremely rare finding in children (Table 3). We presume that increased breast tissue sensitivity locally resulted in unilateral prepubertal gynaecomastia in Sibling 1.

Both siblings had prepubertal testicular enlargement in the absence of a discrete mass, without evidence of central or peripheral precocious puberty or LCCSCT. Testicular biopsy findings have been reported in eight children with PJS and bilateral testicular enlargement. There were no gross abnormalities, but there were clusters of expanded seminiferous tubules containing large Sertoli cells, suggestive of multifocal intratubular neoplasia of large Sertoli cells, different to LCCSCT histology[2].

This *STK11* variant (910C>T) has previously been described in families with PJS. Published cases report presentation in adolescence with gastrointestinal symptoms secondary to polyps, with and without mucocutaneous pigmentation and a positive family history[3,4,5].

Table 3: Causes of prepubertal gynaecomastia & macro-orchidism

Causes of prepubertal gynaecomastia	
Unilateral	**Bilateral**
Lipoma	Obesity
Primary breast tumour	Medications e.g. anti-psychotics
Dermal exposure to oestrogen-containing substances	Dermal exposure to oestrogen-containing substances
Increased breast tissue sensitivity	Increased breast tissue sensitivity
	Feminising adrenal/ testicular tumours
	Aromatase excess syndrome
	46,XX testicular DSD
	PAIS
Causes of prepubertal macro-orchidism	
Unilateral	**Bilateral**
Testicular tumour	Central precocious puberty
Leydig cell hyperplasia e.g. testotoxicosis, McCune Albright Syndrome (MAS)	Severe hypothyroidism
	Leydig cell hyperplasia e.g. testotoxicosis, HCG secreting tumour, MAS
Sertoli cell hyperplasia e.g. MAS	Sertoli cell hyperplasia e.g. MAS, PJS
	Testicular adrenal rest tumours
	Lymphoma
	IGSF1 deficiency