Case Report

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Possible hints and pitfalls in diagnosing Peutz-Jeghers syndrome

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Abstract

Background: Peutz-Jeghers syndrome (PJS) is characterized by gastrointestinal polyposis, mucocutaneous pigmentation and cancer predisposition. Patients with PJS can develop large calcifying Sertoli cell tumors (LCSTs).
Case presentation: A patient presented at 3 years of age with delayed development, hypermobility and later also with tall stature and advanced bone age. Extensive endocrine evaluation, mutation analysis of genes associated with connective tissue disorders and a single nucleotide polymorphism (SNP) array showed no abnormalities. At 8 years of age, gynecomastia developed as well as pigmentations on the lips, both of which are associated with PJS. Mutation analysis showed a heterozygous deletion of the whole *STK11* gene confirming PJS. Testicular ultrasound confirmed the presence of LCSTs. Interestingly, the previously performed SNP array did not report deletion of the *STK11* gene.
Conclusions: We advise excluding LCSTs in children with tall stature and advanced bone age where more common causes have been eliminated. Although *STK11* deletions are documented in control databases, reporting the deletion of this gene even in the absence of a phenotype is advised for patient management.

Keywords: gynecomastia; Peutz Jeghers syndrome; Sertoli cell tumors; *STK11*; tall stature.

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Introduction

Peutz-Jeghers syndrome (PJS) is a rare condition characterized by gastrointestinal polyposis, mucocutaneous pigmentation and cancer predisposition [1]. Most patients with PJS present between 6 and 18 years of age with symptoms of obstruction due to small intestine intussusception [2]. Some patients with PJS develop sex-cord tumors known as large calcifying Sertoli cell tumors (LCSTs) [3, 4].

The diagnosis of PJS is based on clinical findings or identification of a heterozygous pathogenic variant in the *STK11* gene [1, 2]. In approximately one-third, a partial or whole gene deletion can be found [5, 6].

We present a patient exhibiting a wide variety of clinical manifestations of PJS, which illustrates the difficulty of diagnosing this syndrome at an early age. Furthermore, we present data exposing the pitfalls of using control databases in determining the pathogenicity of copy number variations (CNVs).

Case presentation

The patient is the third child of non-consanguineous parents. He was born full term. His birth weight was 3910 g (0.6 standard deviation score [SDS]) and his birth length 52 cm (0.4 SDS). During infancy, he had an umbilical hernia that was surgically corrected. Psychomotor development was mildly delayed particularly regarding gross motor skills for which physical therapy was started. Speech development and fine motor skills were normal.

At 3.5 years of age, he was referred to the clinical geneticist because of hypermobility (Figure 1A). Gross motor skills were improving with physical therapy. His height was 107.2 cm (1.7 SDS) (Figure 2), weight 15 kg (–2.5 SDS weight for height) and head circumference 50 cm (–0.5 SDS). His father's height was 181 cm (–0.4 SDS) and his mother's was 171 cm (0.0 SDS). Family history was positive for aortic aneurysm in his maternal grandfather, but no other abnormalities were noted, including tall

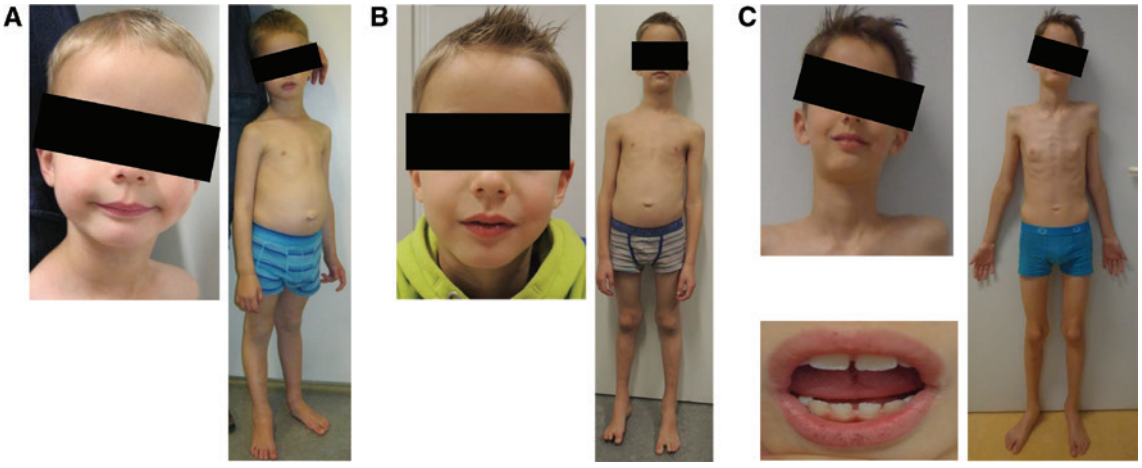

Figure 1: Physical characteristics of the patient at 3.5 (A), 6 (B) and 8 (C) years of age. Note the pigmentations on his lips and the gynecomastia in Figure 1C. Pictures published with permission of the parents.

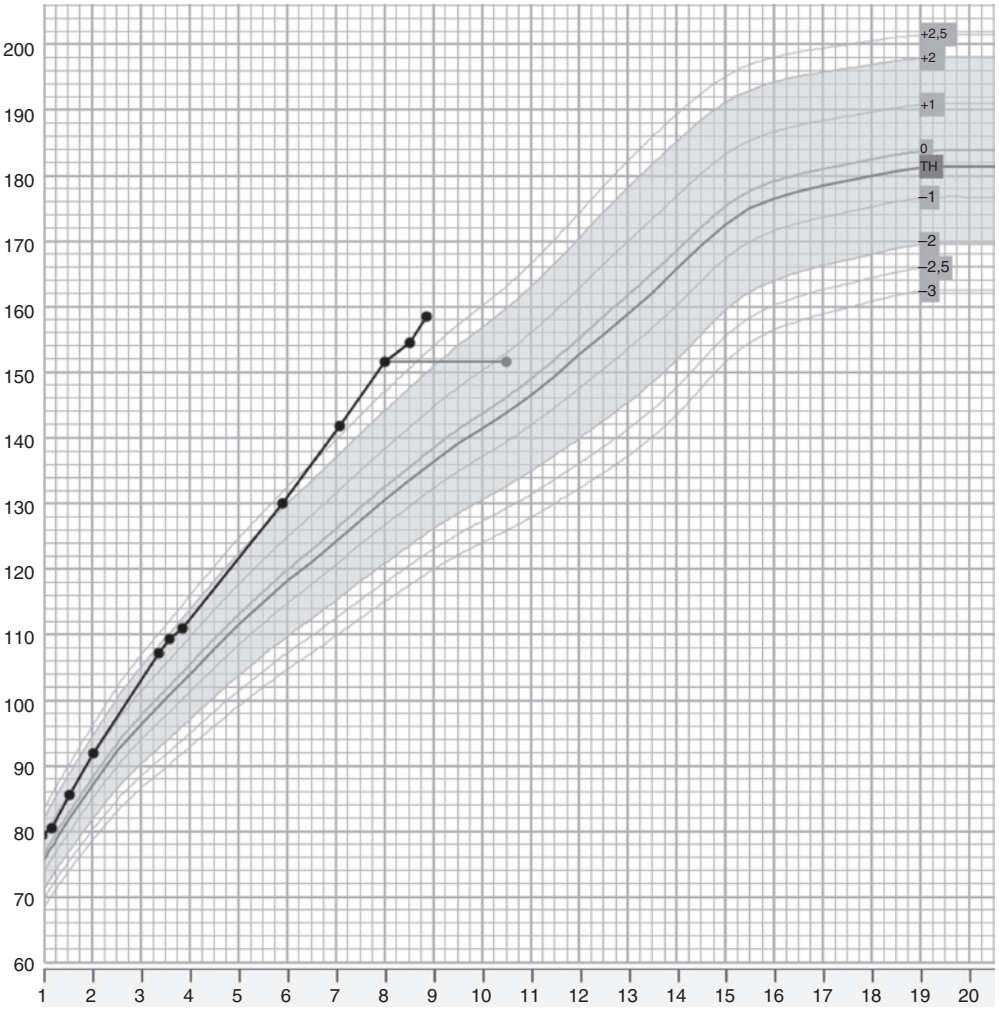

Figure 2: Growth chart.
At 8 years of age, bone age is 2 years and 4 months advanced. Target height (TH) is 181.4 cm.

stature or hypermobility. Physical examination showed a downslant, retrognathia, a high palate, joint hypermobility (Beighton score 6/9), mild scoliosis and pes planus. Cardiovascular examination showed an aortic root that was in the normal to high range. There was no ectopia lentis. Because of the hypermobility and a normal to high aortic root in combination with some features of Marfan syndrome, mutation analysis of the *FBN1* gene was performed and was negative.

The patient was reevaluated at 6 years of age (Figure 1B). Psychomotor development was improving. He was attending a regular primary school. Height was 130 cm (2.2 SDS), sitting height to height ratio 0.51 (–1.8 SDS), arm span 127 cm, weight 22 kg (–2.4 SDS weight for height) and head circumference 52 cm (0.2 SDS). Physical examination showed upward growth of anterior hair, frontal bossing, downslant, mild asymmetry of the chest, scapula alata, joint hypermobility (Beighton score 8/9), pes planus and soft skin. Cardiovascular examination showed an aortic root stable in the normal to high range. The above described symptoms were suggestive of a connective tissue disorder. However, mutational analysis of the *ADAMTS2, CHST14, COL1A1, COL1A2, COL5A1, COL5A2, PLOD1, SLC39A13, TNXB* and *ZNF469* genes showed no abnormalities. Because of his tall stature, mild delay in development, hypermobility and dysmorphic features, an Affymetrix CytoScan HD SNP array (Thermo Fisher Scientific, Waltham, MA, USA) was performed. An interstitial duplication of approximately 383 kb on chromosome 10 (127.744.011–128.127.151 [GRCh37]) was found. The same duplication was found in his healthy father, thus most likely not explaining the phenotype.

During the following years, he was seen by a pediatric endocrinologist for his tall stature. Overall blood and endocrine examination showed no abnormalities. His bone age was 2 years advanced.

At 8 years of age, he developed bilateral, symmetric gynecomastia without nipple discharge, and the height SDS increased further (Figure 1C). Height was now 151.7 cm (3.3 SDS) (Figure 2). His testis appeared to be early pubertal (4–5 mL), no scrotal mass was palpated or pain reported. His penis appeared long for his age and pubertal stage. Neurological, cardiovascular, respiratory and abdominal examinations were normal. Extensive endocrine evaluation revealed no abnormalities (particularly estradiol <18 pmol/L). Bone age was 2.5 years advanced.

After 6 months of follow-up, melanotic pigmentations on the lips became apparent. No pigmentation was visible on his hands, feet or genitalia. The combination of buccal mucosa freckling, accelerated growth and gynecomastia has been described in PJS and Carney complex, and mutation screening of the *STK11* and *PRKAR1A* genes was performed [7]. Using multiplex ligation-dependent probe amplification (MLPA), a heterozygous deletion of the whole *STK11* gene was found consistent with Peutz-Jeghers syndrome. No mutations were found in the *PRKAR1A* gene associated with Carney complex. Reassessment of the single nucleotide polymorphism (SNP) array data confirmed a deletion of approximately 217 kb on chromosome 19p13.3 including *STK11* and nine other genes (Figure 3). The patient's family history revealed no family members with precocious puberty, early breast development, cancer, polyps in the intestine or PJS. Evaluation of the SNP array data in both healthy parents showed no deletion on chromosome 19p13.3, indicating that the deletion was *de novo*.

A scrotal ultrasound was performed showing multiple calcifications varying in size (max. 1.5 mm) consistent with LCSTs. There were no signs indicating a neoplasia (e.g. abnormal vascularization). At present, our patient is being monitored on a regular basis. According to current clinical guidelines, a colonoscopy and upper gastrointestinal endoscopy will be performed.

Discussion

PJS is an autosomal dominant inherited disorder and is caused by a heterozygous mutation in the *STK11* gene that encodes a serine-threonine kinase. This serine-threonine kinase functions as a tumor suppressor [1]. The diagnosis of PJS is based on clinical findings or confirmed by finding pathogenic mutations in the *STK11* gene. This gene is located on chromosome 19p13.3. In 73–94% of PJS patients, a mutation in the *STK11* gene can be found [1, 2, 5, 6]. All types of variants have been reported, from missense variants to whole-gene deletions and also larger microdeletions of the 19p13.3 region [7].

Hallmark features of PJS are diffuse gastrointestinal polyposis, mucocutaneous pigmentation and a predisposition to develop a wide variety of cancers [1, 2]. Patients with PJS usually present with gastrointestinal symptoms or present because of affected family members. However, as illustrated by our patient, PJS patients can present with growth acceleration and gynecomastia due to LCSTs [3, 4, 8–15]. The LCSTs overexpress p450 aromatase resulting in increased production of estradiol. The elevated levels of estradiol stimulate skeletal growth and breast development [16]. Notably, in our patient, estradiol levels were not increased. This has previously been described by Coen et al. and Crocker et al. [4, 17]. They postulate

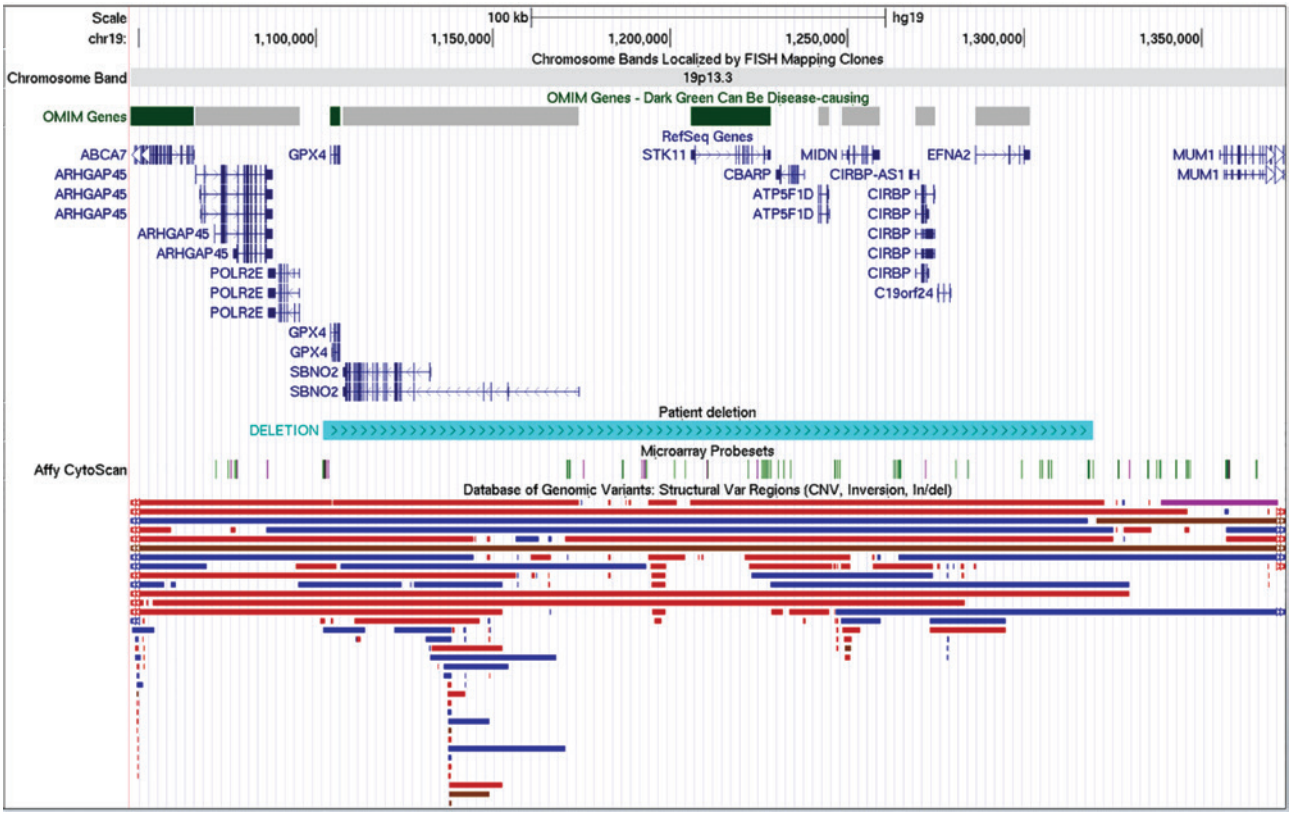

Figure 3: University of California Santa Cruz (UCSC) genome browser screenshot of the 19p13.3 deletion region including *STK11* and nine other genes (*SBNO2*, *EFNA2*, *CIRBP*, *ATP5D*, *C19orf26*, *MUM1*, *GPX4*, *MIDN* and *C19orf24*).
The genomic coordinates of the deletion are 1.102.063–1.319.319 in GRCh37 assembly. The bottom tracks show the structural variation regions of one or more healthy individuals collected in the Database of Genomic Variants (red bars are deletions, blue bars duplications, magenta bars inversions and brown bars all of the above).

that this might be explained by the detection limits of standard assays. Also, in men, the majority of estradiol (>80%) is produced by extragonadal aromatization and only a small fraction is secreted by the testis. Thus, a substantial increase in testicular production of estradiol will add little to the serum concentration. Nonetheless, the sensitivity of the growth plates and breast tissue to estrogens still leads to growth acceleration, advanced bone age and breast development [4, 17]. The persistent estrogen stimulation can lead to premature closure of the epiphyses and ultimately to short stature [18, 19]. Based on these data, one might consider performing testicular ultrasound to exclude LCSTs in children with tall stature and advanced bone age where more common causes have been eliminated.

LCSTs are usually reported to be benign and there is a low risk of malignant transformation. Based on expert opinion only, a conservative approach is recommended with annual testicular examination. In patients where an abnormality is found on ultrasound or precocious puberty develops an ultrasound can be performed yearly [1]. Aromatase inhibitors have been used to reduce gynecomastia and prevent premature closure of growth plates. Recently, a larger number of patients were reported [17]. This study found that patients with LCSTs benefit from treatment with an aromatase inhibitor with reduction and/or elimination of gynecomastia and slowing of linear growth and bone age advancement. The use of an aromatase inhibitor was considered in our patient. However, as gynecomastia was minimal and he did not experience any psychological distress, no aromatase inhibitor therapy was initiated. In addition, even if premature closure of the epiphyses would occur, his adult height is still expected to be within the normal range.

Interestingly, at 6 years of age, an SNP array was performed that did not report the deletion on chromosome 19p13.3. After reevaluation of the SNP array data at 8.5 years of age, the deletion involving the whole *STK11* gene was confirmed. However, as at 6 years of age the phenotype was not consistent with PJS and deletion of the whole *STK11* gene had been described in several reference databases, this deletion was not reported. This

shows a possible pitfall of control databases in determining the pathogenicity of CNVs. There are several plausible explanations. First, it could be that the persons in the reference databases are underdiagnosed. The database of genomic variants reports nine healthy individuals with whole *STK11* gene deletions, as does the Welcome Trust Case Control Consortium [20, 21]. Of these 18 healthy individuals the exact age is unknown, but subjects are all 18 years or older. However, as clinical features of PJS are usually severe and typically appear in childhood (excluding malignancies), underdiagnoses seem less likely. A second option might be that reduced penetrance (to a certain age) is more frequent than expected. However, up until now only one case of nonpenetrance has been described [22]. In addition, a clear genotype-phenotype correlation has not been demonstrated in subject with PJS. With regard to cancer risk, Hearle et al. reported that the type and site of mutation did not influence cancer risk [23]. Reduced penetrance might also be explained by the effect of possible modifiers. Papp et al. suggested that deletions extending upstream of *STK11* into *GPX4* might serve as a protective factor leading to a later age of PJS symptom onset [24, 25]. Based on these data, we advise DNA laboratories to reassess their SNP array data on the occurrence of *STK11* gene deletions and whether they are classified as likely benign as this might have implications for health prognosis and surveillance in patients.

There are no typical dysmorphic features described in patients with PJS other than the mucocutaneous freckling. Our patient presented not only with accelerated growth and tall stature, but also with frontal bossing, soft skin and joint hypermobility. To our knowledge, this has not been described in the literature. Scollon et al. and Kuroda et al. did suggest that 19p13.3 microdeletions encompassing not only *STK11* but also other neighboring genes might be responsible for mild developmental delays and distinctive features including a broad forehead. However, the genes suggested to be involved by Kuroda et al. (e.g. *ARID3A* and *PTBP1*) do not overlap with our patient [25, 26]. At this point, we do not think that the features described in our patient can be fully explained by the deletion that was found.

Conclusions

We describe a patient with PJS who initially presented with tall stature and advanced bone age, and later also with gynecomastia due to LCSTs. We suggest screening for the presence of LCSTs in children with tall stature and advanced bone age when more common causes have been excluded. Also, we expose a possible pitfall of control databases in determining the pathogenicity of CNVs. We advise reporting deletion of the *STK11* gene even in the absence of a phenotype as this is important for patient management.

Learning points

- Diagnosing PJS at an early age can be difficult. Some patients present with tall stature and advanced bone age
- Consider screening for the presence of LCTS's in patients with tall stature and advanced bone age when more common causes have been excluded and an underlying condition is suspected
- Control databases can underestimate the pathogenicity of copy number variations. We advise reporting deletion of the *STK11* gene even in the absence of a phenotype.

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