Unusual association of diseases/symptoms

A child with an STK11 mutation and Sotos syndrome-like features: can STK11 mutations produce a Sotos syndrome phenocopy?

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In accordance with interrelationships between tumour predisposition and somatic overgrowth, the authors present a boy with a familial serine threonine kinase 11 (STK11) mutation and Sotos syndrome-like features. The authors suggest that, analogous to phosphatase and tensin homolog mutations, STK11 mutations may predispose to somatic overgrowth. In a minority of instances, this may result in a Sotos syndrome phenocopy. If substantiated, this observation may yield insights into both the molecular causes of tumour predisposition and overgrowth syndromes.

BACKGROUND

The molecular causes of bowel polyposis, associated cancers and syndromic overgrowth remain undetermined in a significant proportion of individuals. We present this case to suggest that (1) consideration needs to be given to investigate for mutations in genes associated with polyposis syndromes in those with overgrowth conditions without known molecular cause, and (2) mutations in genes associated with syndromic overgrowth could be sought in individuals with polyposis in whom mutations in genes generally known to be associated with these conditions have not been detected. Ultimately this may result in more appropriate individual care.

CASE PRESENTATION

A 4-year-old boy was referred with bilateral intratubular sertoli cell proliferations and a family history of Peutz-Jeghers syndrome (PJS) associated with a known serine threonine kinase 11 (STK11) mutation, c.180C> A p.Tyr60X. The parents were non-consanguineous Caucasian Australians and maternal and paternal ages were 26 and 28 years, respectively. The couple had two previous pregnancies including one first trimester spontaneous abortion. There was no known teratogen exposure. First trimester screening for aneuploidy gave a low-risk result and a fetal ultrasound anatomy survey revealed a dichorionic diamniotic twin pregnancy. The proband was delivered by elective caesarean section at 36 weeks, with a birth length of 48 cm (more than two SD above the mean for a twin pregnancy), a birth weight of 2460 grams (25–50th percentile) and a head circumference of 34.5 cm (just below the 90th centile). The neonatal period was unremarkable aside from jaundice treated with phototherapy.

Developmentally, he had mild motor and language delay, rolled at 6 months, crawled at 10 months and walked at 2 years of age. He was receiving speech and occupational

therapies. He was shy and had difficulty interacting with his peers.

The family history was notable for the proband's mother's STK11 mutation (figure 1), which in her was associated with multiple gastrointestinal polyps, and that she was a presumed dizygotic twin.

At 4-years-of age, the proband was shy but cooperative. He had a height of 112.4 cm (above the 97th centile), a head circumference of 53 cm (just below the 97th centile), long and downslanting palpebral fissures, a triangular face with pointed and prominent chin, prominent forehead (figure 2), deep-set eyes, mild scaphocephaly, high and narrow palate (figure 3b). Additionally, he had mild hypotonia with pes planus, medial rotation of the medial malleolus and mild joint hyperlaxity. Cardiac and renal examinations were normal. There was gynaecomastia but no mucosal hyperpigmentation. On review at 5 years of age, malar flushing (figure 3a) was noted; there were otherwise no new features. The mother's height was 171.2 cm (75th–90th percentile) and the father's height was 180.1 cm (75th centile). The proband's parents had no overt features of Sotos syndrome either as adults or children.

INVESTIGATIONS

At the time of presentation with gynaecomastia at 4 years of age, the bone age was 5 years (SD of 6.66 months) and serum α fetoprotein, estradiol, follicle-stimulating hormone, luteinizing hormone and beta subunit of human chorionic gonadotropin were normal. Testing confirmed that the proband had the familial STK11 mutation.

The following genetic investigations were normal: G-banded karyotype at the 550 band level, subtelomere fluorescence insitu hybridisation on metaphase spreads, using the Totelvision subtelomere screening kit (Vysis, Downers Grove, Illinois, USA), Fragile-X sequencing, 11p15 region methylation sensitive multiplex ligation-dependent probe

Figure 1 Pedigree showing phenotype and serine threonine kinase 11 (STK11) genotype in the family.

Figure 2 Proband at 4 years of age showing long down slanting palpebral fissures, a triangular face with pointed and prominent chin and a prominent forehead.

amplification (MLPA) (SALSA MLPA kit, MRC-Holland), nuclear SET domain 1 (NSD1) mutation analysis was performed using a combination of genomic DNA (gDNA) and complementary DNA (cDNA) amplification followed by sequencing. Exons 3 to 23 of NSD1 were amplified from cDNA by PCR in a total of eight overlapping fragments. Exons 2, 3, 6, 7, 8 and 9 were also amplified by PCR from gDNA. Additionally, NSD1 MLPA was performed (SALSA MLPA kit P026, MRC-Holland). No neuroimaging, cardiac or renal ultrasound had been performed.

DISCUSSION

Some familial cancer/bowel polyposis predisposing conditions may be associated with syndromic features, including localised or generalised overgrowth, which facilitate their recognition and subsequent targeted surveillance to reduce tumour-related morbidity and mortality. The presence of tumour predisposition in some syndromic overgrowth conditions, including Sotos syndrome, supports aetiological overlap of tumour predisposition and somatic overgrowth. However, the molecular causes of syndromic overgrowth and familial cancer predisposition remain undetermined for a significant number of individuals. We present the first reported case in which a Sotos syndrome-like phenotype was associated with an STK11 mutation. STK mutations are known to be associated with the bowel polyposis syndrome PJS, a condition for which somatic overgrowth is not part of the known phenotype. We suggest that in a minority of instances, STK11 mutations may

Figure 3 Photographs at 5 years of age showing malar flush (a) and a high palate (b).

result in a Sotos syndrome-like disorder (phenocopy) and if so, this may yield insights into tumorigenesis and somatic overgrowth.

Our patient may coincidentally have two rare conditions one of which is associated with an undetected mutation in the NSD1 (Sotos syndrome) gene or another gene. In time, clinical investigation of these possibilities may be facilitated by emerging technologies, including next generation sequencing, that allow for simultaneous targeted assessments of multiple candidate genes or exome/genome wide assessments. These techniques are currently largely employed in research programs and significant interpretative challenges remain. A second possibility is that mutations in STK11 may rarely result in a Sotos syndrome phenocopy. Notably, Ruvalcaba initially thought his cases with intestinal polyposis and pigmentary changes of the genitalia, which were subsequently diagnosed with Bannayan-Riley-Ruvalcaba (BRR) syndrome, had Sotos syndrome, and BRR is associated with phosphatase and tensin homolog (PTEN) mutations which is a known cause of bowel polyposis. Also notable in the context of this case, is that PJS was considered in the differential diagnosis,¹ furthermore, PTEN mutations can be associated with features overlapping with Sotos syndrome, including macrocephaly and learning difficulties,² and with cancers, including breast and thyroid cancer, which also occur in those with STK11 mutations.³ These findings, when taken together with the reported case, suggest that genes associated with intestinal polyposis syndromes might account for a minority of cases of Sotos syndrome-like phenotypes and supports interrelations between syndromic overgrowth and intestinal polyposis conditions.

Mechanistically, STK11 is ubiquitously expressed, has STK activity and has multiple substrates, including 5' adenosine monophosphate-activated protein kinase and tuberlin, that have been implicated in its signalling.⁴ NSD1 is a corepressor and coactivator of transcription which is possibly associated with chromatin architecture.⁵ There is no direct evidence that these genes interact, however, given their functions and ubiquitous substrates it is possible that there are overlaps in their downstream signalling. Tumour suppressor genes, including STK11, PTEN, tuberous sclerosis protein 1 (TSC1) and TSC2, have convergent networks, including β -catenin pathways.⁶ It is possible that disruption of these convergent networks at varying sites might have overlapping phenotypic consequences. Accordingly, an individual with Sotos syndrome, with an NSD1 deletion, and multiple giant pilomatricomas has been described⁷ and pilomatricoma is associated with somatic β -catenin mutation in 75% of patients.⁸ It is therefore conceivable that multiple pilomatricomas may be consistent with a perturbation of the β -catenin pathway by this patient's NSD1 mutation.

In conclusion, our patient may have two independent conditions, or his features might support interrelationships between the genetic causes of syndromic overgrowth and tumour predisposing conditions. We suggest consideration be given to (1) Investigating for mutations in genes associated with polyposis syndromes in those with overgrowth of unknown cause, and (2) investigating for mutations in genes associated with syndromic overgrowth in individuals with polyposis, in whom mutations in genes generally known to be associated with these conditions have not been detected. Ultimately, this may facilitate improved patient care.

Learning points

- ▶ A thorough history and careful clinical examination, with consideration to syndromic causes of cancer, need to be performed in all individuals with cancer. This should include ascertainment of height, weight and head circumference.
- ▶ Consideration should be given to investigate for mutations in genes associated with polyposis syndromes in those with overgrowth of unknown cause.
- ▶ Consideration should be given to investigate for mutations in genes associated with syndromic overgrowth in individuals with polyposis, in whom mutations in genes generally known to be associated with these conditions have not been detected.

Competing interests None.

Patient consent Obtained.

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