SF1 mutation - a rare cause of pubertal androgenisation

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Case history
A 14-year-old Caucasian girl presented to clinic with a history of delayed puberty. Clinical examination revealed facial and axillary hair, with absent breast development. She refused permission for genital examination but indicated she felt there were genital abnormalities present. There was no history of ambiguous genitalia at birth or in childhood. She was reluctant to undergo any investigations, but eventually gave consent to limited tests, imaging and, after 12 months, an examination under anaesthesia.

Investigations and results
Initial blood tests showed a high testosterone level (22.6nmol/L), with a high testosterone: dihydrotestosterone ratio (14:1) and a low oestradiol level (99pmol/L). Her karyotype was 46 XY.
Pelvic imaging showed inguinal gonads but no uterus. Subsequent examination under anaesthesia revealed extensive virilisation with 6cm x 2cm clitoromegaly, a narrow 7cm vagina and a common urogenital opening.
The biochemical and clinical picture suggested a differential diagnosis of 5-alpha reductase deficiency, partial androgen insensitivity or 17-beta hydroxysteroid-dehydrogenase deficiency; a urine steroid profile however was normal, and genetic mutation analysis for these conditions was negative. Subsequent analysis of the NR5A1 gene, encoding the SF1 protein, demonstrated a heterozygous mutation within exon 5.

Treatment
After significant counselling the patient stated her desire for a female identity, undergoing laparoscopic gonadectomy and clitoral reduction. Oestrogen replacement therapy was commenced.

Conclusions and points for discussion
This case highlights a rare cause of pubertal androgenisation. The NR5A1 gene is expressed in undifferentiated gonads, and there is wide phenotypic variation in patients with an XY karyotype and NR5A1 gene mutations. This case is a previously unreported presentation of a mutation in this gene. It was particularly challenging because of the young girl’s reluctance to engage, and she and the family received intensive psychological and medical support. Following surgery the girl is noticeably happier and regularly attends hospital appointments.