Molecular Diagnosis of 5α-Reductase Deficiency in 4 Elite Young Female Athletes Through Hormonal Screening for Hyperandrogenism

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Context: Although a rare occurrence, previously undiagnosed disorders of sex development (DSD) with hyperandrogenism are sometimes detected by hormonal screening during the international sports competitions. Identifying the cause of XY,DSD raises medical and ethical concerns, especially with regard to issues of the eligibility to compete.

Objective: The aim of this study was to determine whether the detection of high plasma T in young elite female athletes during hormonal screening would reveal an unsuspected XY DSD.

Setting: The study was performed in the Nice and Montpellier University Hospitals (France), which collaborate as reference centers for DSD in elite athletes on behalf of sports governing bodies.

Patients: Four cases of elite young athletes with female phenotypes but high plasma T detected during hormonal screening were investigated for undiagnosed XY DSD.

Main Outcome Measures: Evaluation of clinical, biological, radiological (magnetic resonance imaging and dual-energy x-ray absorptiometry) and genetic characteristics was conducted.

Results: The 4 athletes presented as tall, slim, muscular women with a male bone morphotype, no breast development, clitoromegaly, partial or complete labial fusion, and inguinal/intralabial testes. All reported primary amenorrhea. The hormonal analysis evidenced plasma T within the male range, the karyotype was 46, XY, and molecular analysis of the 5α-reductase type 2 (*srd5A2*) gene identified a homozygotic mutation in 2 cases, a heterozygotic compound in 1 case, and a deletion in 1 case.

Conclusion: 5α-Reductase deficiency should be investigated in elite young female athletes with primary amenorrhea and high male T levels detected during antidoping programs to identify undiagnosed XY DSD. (*J Clin Endocrinol Metab* 98: E1055–E1059, 2013)

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Diagnosis of 5α-Reductase 2 Deficiency: Is Measurement of Dihydrotestosterone Essential?

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BACKGROUND: 5α-Reductase 2 deficiency (5ARD) is a known cause of 46,XY disorders of sex development (DSD). Traditionally, the diagnosis relies on dihydrotestosterone (DHT) measurement, but the results are often equivocal, potentially leading to misdiagnosis. We reviewed alternative approaches for diagnosis of 5ARD.

METHODS: We conducted a retrospective review of the results of urinary steroid profiling (USP) by GC-MS and mutational analysis of *SRD5A2* [steroid-5-alpha-reductase, alpha polypeptide 2 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 2)] by PCR and direct DNA sequencing of all 46,XY DSD patients referred to our laboratory with biochemical and/or genetic findings compatible with 5ARD. We also performed a literature review on the laboratory findings of all 5ARD cases reported in the past 10 years.

RESULTS: Of 16 patients diagnosed with 5ARD between January 2003 and July 2012, 15 underwent USP, and all showed characteristically low 5α- to 5β-reduced steroid metabolite ratios. Four patients had DHT measured, but 2 did not reach the diagnostic cutoff. In all 12 patients who underwent genetic analysis, 2 mutations of the *SRD5A2* gene were detected to confirm the diagnosis. Twenty-four publications involving 149 patients with 5ARD were published in the review period. Fewer than half of these patients had DHT tested. Nearly 95% of them had the diagnosis confirmed genetically.

CONCLUSIONS: 5ARD can be confidently diagnosed by USP at 3 months postnatally and confirmed by mutational analysis of *SRD5A2*. Interpretation of DHT results may be problematic and is not essential in the diagnosis of 5ARD. We propose new diagnostic algorithms for 46,XY DSD.

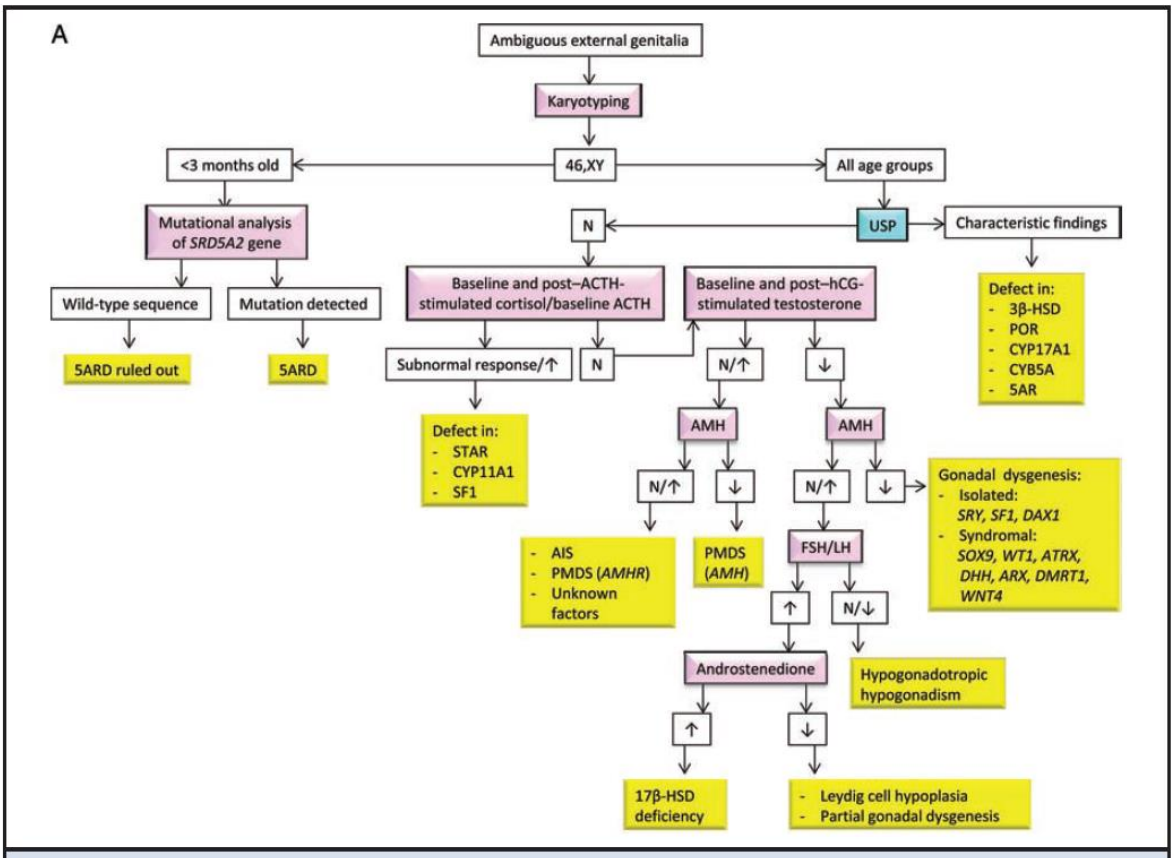

Fig. 2. Proposed diagnostic algorithms for 46,XY disorders of sex development when urinary steroid profiling is readily available (A) and not readily available (B).

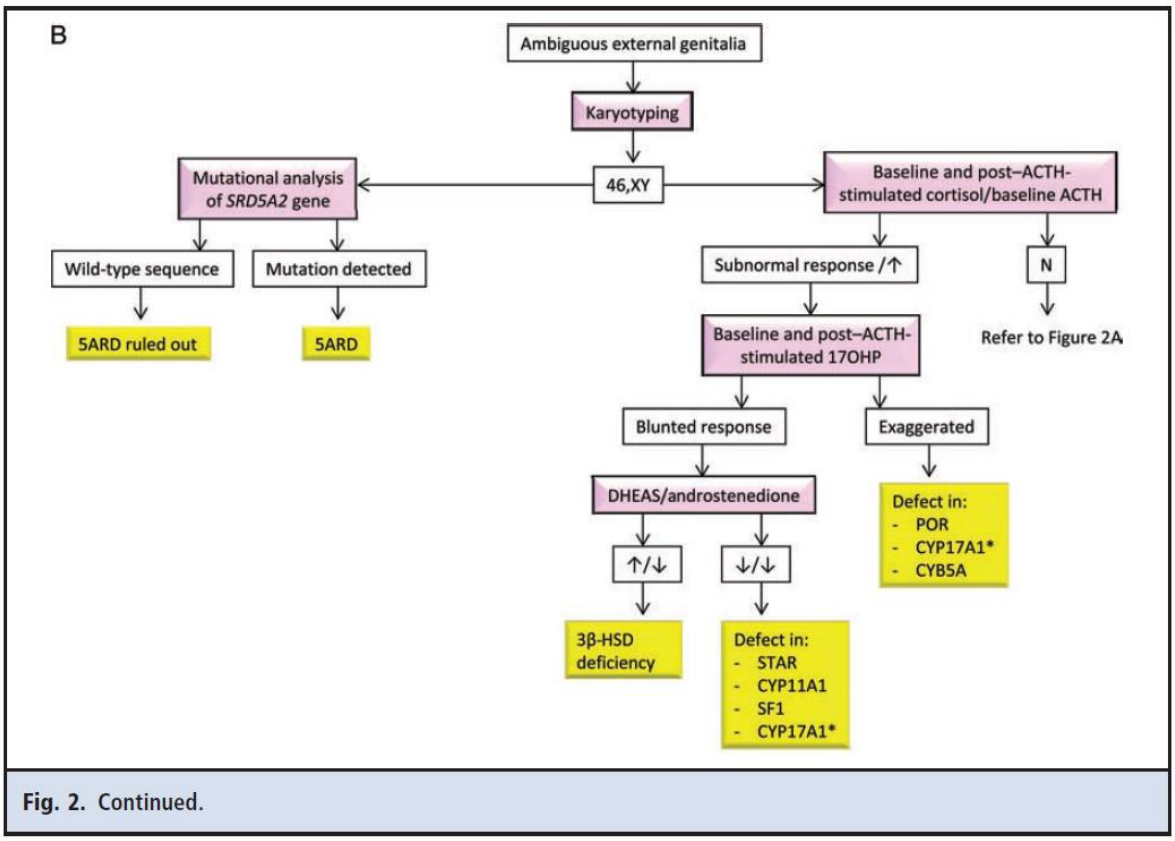

Fig. 2. Continued.