Pubertal virilization in two unrelated XY teenagers with female phenotype due to NR5A1/SF-1 gene mutation

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Background:
Pubertal virilization in a 46,XY DSD patient is generally due to partial androgen insensitivity, 5-alpha-reductase deficiency, or 17-ketoreductase deficiency. Recently, reports have identified virilization signs associated with NR5A1/SF-1 gene mutations.

Cases Presentation and Method:
We present two unrelated cases of pubertal virilization due to NR5A1/SF-1 gene mutation. Both were suspected to be primarily affected by 5-alpha-reductase deficiency but no mutation was identified within the SRD5A2 gene coding sequence. The first case was a young high-level female athlete with biological and clinical signs of hypervirilization. The second case was a girl first investigated in infancy for coalescence of the labia minora. At this time, the karyotype revealed a discordant 46,XY formula. Genetic investigation of the SRD5A2 gene identified no abnormality. When she was 15 years old, her physician observed striking signs of virilization: clitoromegaly, high plasma testosterone (8.2 ng/ml) and high FSH (45 UI/l) contrasting with normal LH (6 UI/l).

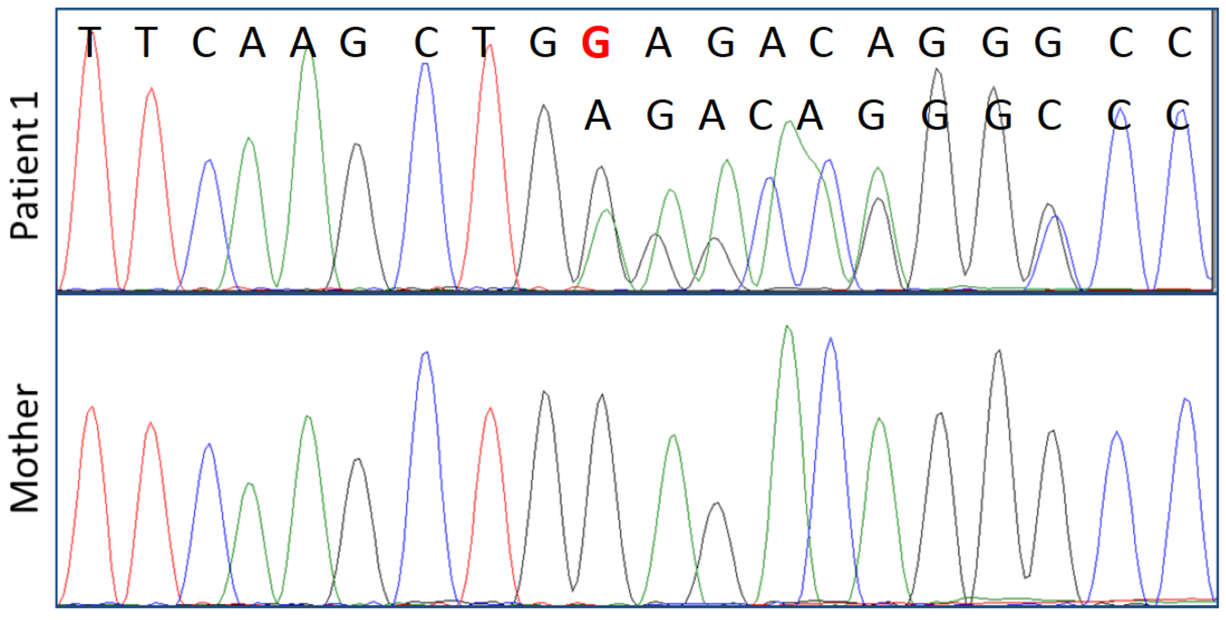

Figure 1: Electrophoregram showing the deletion of nucleotide 361 (lower line : alternative sequence) identified in patient 1

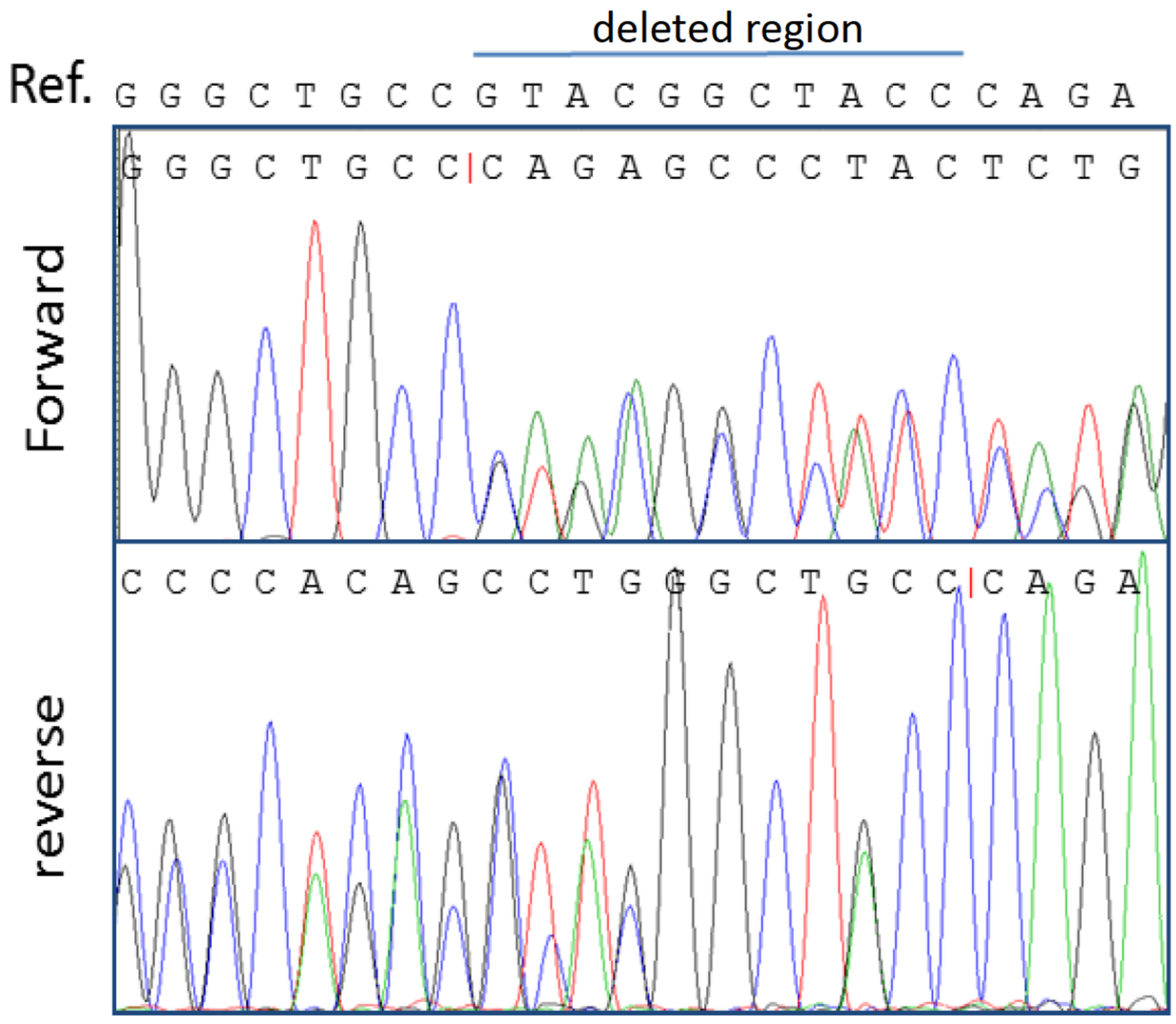

Figure 2: Electrophoregram showing the deletion of 11 nucleotides identified in patient 2

Results:
Genetic investigation of the first case revealed a de novo deletion, c.361delG, in exon 4 that led to a frameshift and premature stop codon p.(Glu121Argfs*175) (Fig. 1). In the second case, we identified an 11-nucleotides deletion (c.630_640delGTACGGCTACC) in exon 4 that led to a frameshift and premature stop codon p.(Tyr211Argfs*11) (Fig. 2). In each patient, the protein, if produced, is truncated and lead probably to incapability of targeted genes transactivation (Fig. 3).

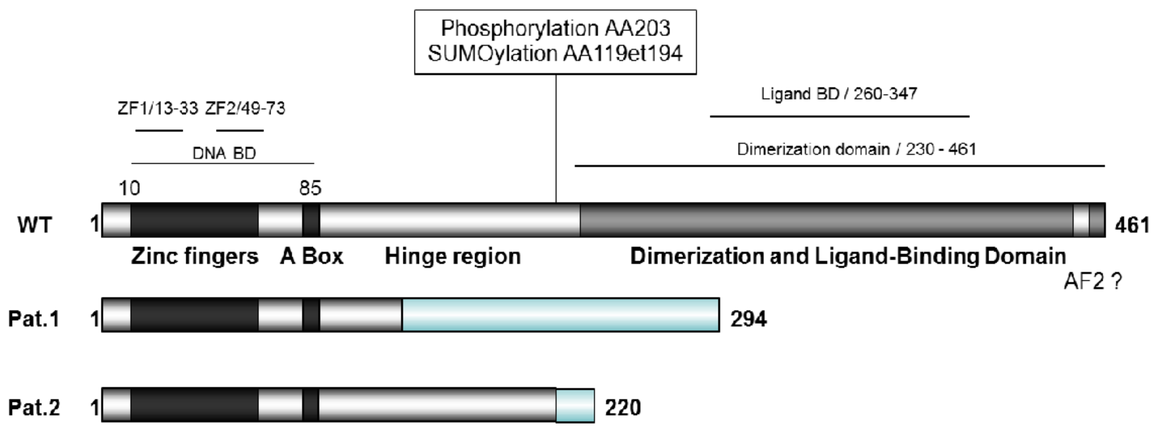

Figure 3: Cartoon showing the WT and mutant proteins. In pale Blue, abnormal protein sequence.

Conclusions:
We report two new NR5A1/SF-1 deletions in 46,XY DSD girls with pubertal virilization. In both cases, the initial diagnosis was 5-alpha-reductase deficiency. In addition to 5-alpha-reductase and 17-ketoreductase deficiencies, these data suggest that NR5A1/SF-1 should systematically be investigated in XY adolescent girls with virilization at puberty.

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