Familial mutation of NR5A1/SF-1 gene associated with 46,XY DSD and spleen agenesis: a new syndrome?

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Background:
A recent report (JCI, 2014) described a new homozygous NR5A1/SF-1 mutation in a patient with 46,XY DSD and spleen agenesis. To date, no other data have confirmed this association, raising the hypothesis of fortuity.

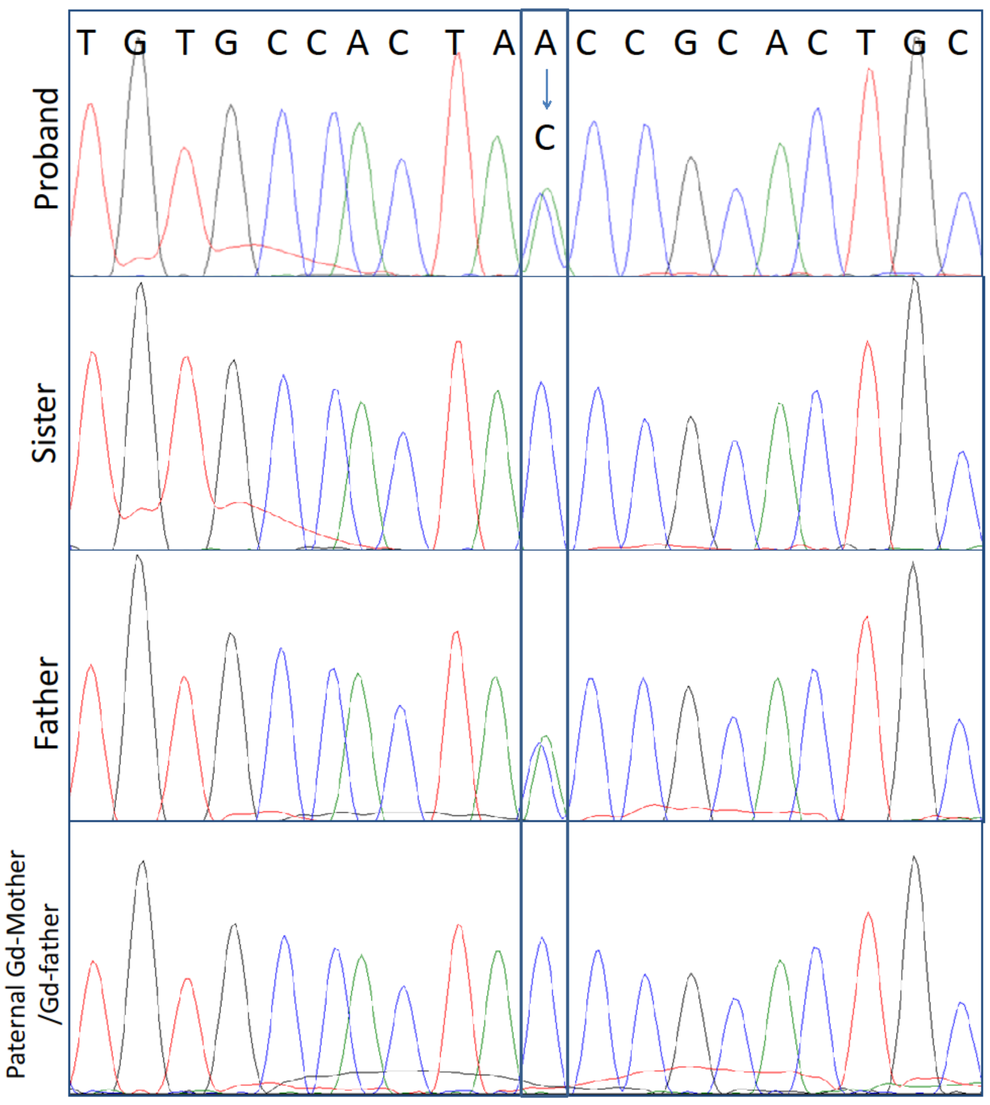

Figure 1: Electrophoregrams of Patient, her sister, her father and grand-parent

Case presentation and method:
We had the opportunity to study an adolescent girl referred for virilization during puberty. At age 12.5 years, she presented voice deepening, moustache and clitoridal hypertrophy. She was overweight. Biological investigations showed high plasma testosterone (2ng/ml) and gonadotropin levels and undetectable levels of AMH and inhibin B. The family history revealed that her father had surgery for hypospadias in infancy. At 45 years, he was hospitalized for purpura fulminans, at which time asplenia was diagnosed.

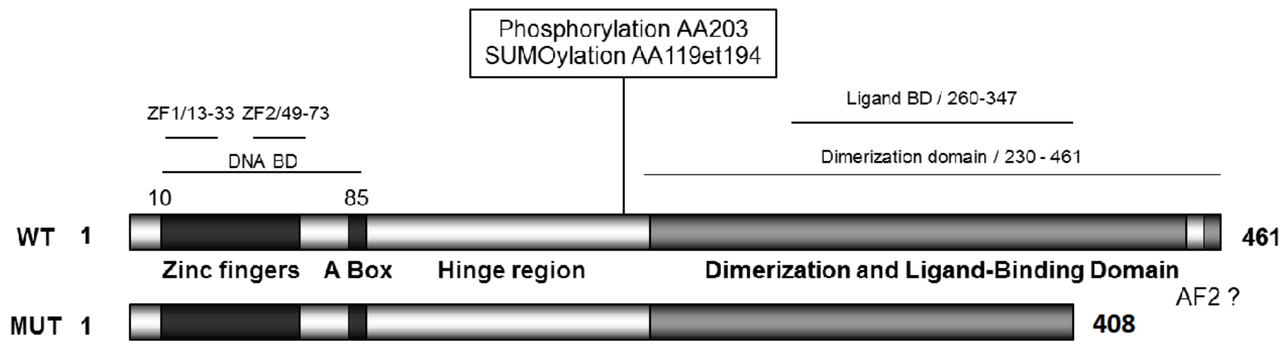

Figure 2: Cartoon showing the WT and mutant protein

Results:
Sonography and MRI showed three small residues which were evocated for spleen. Genetic investigation identified a new heterozygous NR5A1 gene mutation (c.1227C>A) within exon 7. This mutation creates a premature stop codon (p.Tyr409X) and results, if expressed, in a truncated protein (Fig. 2). The father's genetic analysis revealed the same mutation. However, this mutation was absent from both paternal grandparents. In vitro assays of this mutation are in progress to investigate the mutant transactivation capabilities on Tesco (Sertoli), Cyp11a1 (Leydig) and TLX1 (spleen) promoters.

Conclusion:
In mice, SF-1 gene invalidation leads to XY complete gonadal dysgenesis, adrenal agenesis and abnormal spleen development. In human, an SF-1 mutation may lead to both gonadal dysgenesis and spleen hypotrophy, raising the hypothesis of a new syndrome. These data underline the usefulness of spleen function investigation in all patients with SF-1 gene mutation.

Reference:
Zangen D, Kaufman Y, Banne E, Weinberg-Shukron A, Abulibdeh A, Garfinkel BP, Dweik D, Kanaan M, Camats N, Flück C, Renbaum P, Levy-Lahad E. Testicular differentiation factor SF-1 is required for human spleen development.2014. Journal of clinical investigation. 2014. 124 (5): 2071-2075

DOI: 10.3252/pso.eu.54espe.2015