Multi-system Endocrine Disorders

The Founder Homozygous *NR5A1* Gene Mutation p.R103Q Causes Asplenia and Severe XY-DSD and XX-DSD in a Palestinian Cohort

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INTRODUCTION

Mutations in Steroidogenic factor 1 (*SF-1*; also known as *NR5A1*), a transcription factor involved in sexual differentiation, steroidogenesis and reproduction, have been associated with mild to severe XY and XX DSDs and adrenal failure. Asplenia and complete XY sex reversal were recently reported in a Palestinian patient homozygous for p.R103Q *NR5A1* mutation.

CLINICAL CASES

- Five Palestinian girls (three 46, XY and two 46, XX) from 3 unrelated families presented between 13-15 years of age with absence of spontaneous pubertal development and primary amenorrhea for investigations. Three cases had 46, XY karyotype and female external genitalia. They had a significant history for infectious diseases (e.g. pneumococcal sepsis at 9 months of age, aseptic meningitis, hepatitis A, suppurative hip arthritis), asplenia, bilateral inguinal dysgenetic or absent testes, rudimentary or absent uterus and undetectable AMH levels. The 2 other cases (sisters) had 46, XX karyotype, hyposplenia, infantile uterus, absence of ovaries in imaging studies and undetected serum AMH.
- Asplenia was recognized only lately in all of the cases except for case 4, where it was diagnosed at age of 6 months. Interestingly all the cases exemplified delayed adrenarche and undetectable levels of Dehydroepiandrosterone, androstenedione, and testosterone. (table 1)
- All five cases had the homozygous *NR5A1* p.R103Q mutation, originating from one founder (1).

	Family 1	Family 2	Family 3		
Family member	L.R	M.R	F.S	RG. S.	RH. S
Karyotype	46, XY	46, XY	46, XY	46, XX	46, XX
Sex of rearing	Female	Female	Female	Female	Female
Clinical Presentation:					
Age at presentation	13.5 yr	13 yr	14.5 yr	14yr	13.3 yr
Diagnosis	•46, XY severe gonadal dysgenesis • Asplenia	•46, XY complete gonadal dysgenesis • Asplenia	•46, XY complete gonadal dysgenesis • Asplenia	•Primary ovarian insufficiency • Asplenia	•Primary ovarian insufficiency •Asplenia
Phenotype	Delayed puberty, absent uterus	Delayed puberty, rudimentary uterus	Delayed puberty, absent uterus	Delayed puberty Small uterus	Delayed puberty Small uterus
Infection history	Pneumococcal sepsis at 9 months of age	Recurrent infections: • Aseptic meningitis • Hepatitis A • Hip suppurative arthritis •Pneumonia	Not documented	Not documented	Pneumonia and sepsis at 6 months
External genitalia	Female	Female	Female	Female	Female
Gonadal position	Bilateral inguinal	Absent	Absent	Not detected by U/S	Not detected by U/S
Gonadal histologic analysis	Normal and abundant Sertoli cells, few Leydig cells	No definitive ovarian or testicular tissue is observed	No definitive ovarian or testicular tissue is observed	Not operated	Not operated
AMH	Not done	Undetectable	Undetectable	Undetectable	Undetectable
Adrenarche	Delayed till age of 14.5y	Delayed till age of 14.5y	Absent pubic hair and axillary hair by age of 14.8 yr	Absent pubic hair and axillary hair by age of 14.8 yr	Absent pubic hair and axillary hair by age of 13.3 yr
DHEAS (0.9-11.6 µmol/l)	<0.41	<0.41	<0.41	<0.41	<0.41

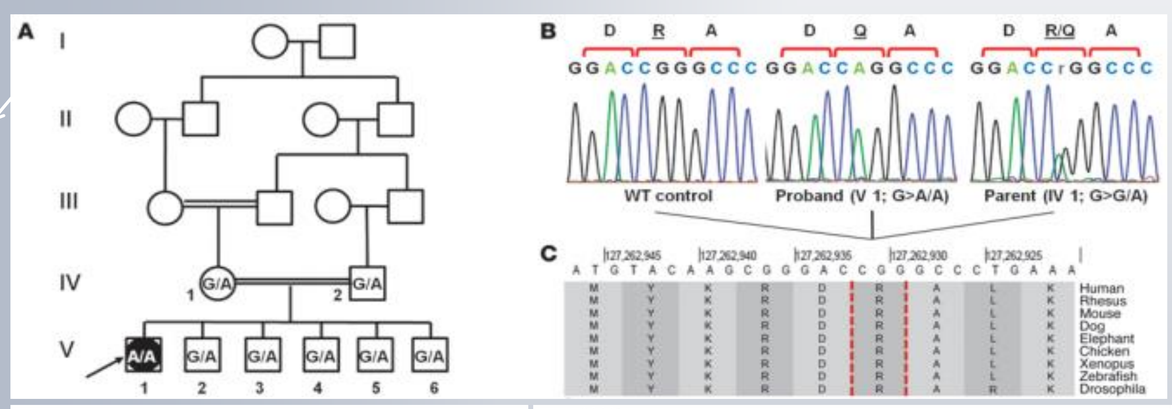

Figure 1: Characterization of the *SF1* mutation in patient 1's family. (A) Pedigree of the patient's consanguineous family. (B) DNA sequencing chromatograms of the c.308G>A mutation (p.R103Q) (C) Cross-species conservation of the residues adjacent to R103 (dashed vertical outlines). Transcriptional activation of spleen-specific (D) and steroidogenic (E) promoters by WT or mutant *SF1* vectors (1).

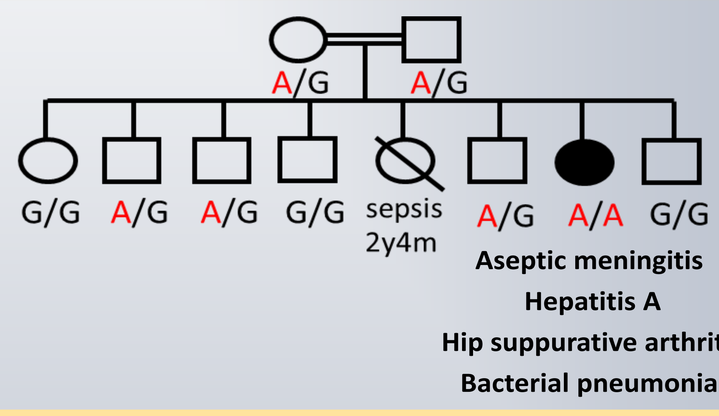

Figure 2: Characterization of the *SF1* mutation in patient 2's family. Patient 2 had a significant past history of recurrent serious infections, and her sister died due to sepsis.

CONCLUSIONS

The homozygous R103Q *NR5A1* mutation causes complete XY sex reversal but also completely disables the development of an ovary. DSD in the context of significant infections should alert to asplenia and NR5A1 mutation, and consequently indicate lifesaving preventive measures such as vaccinations and antibiotic prophylaxis. The undetectable AMH levels in this cohort suggests a critical role of human SF-1 in AMH transcription. The delayed adrenarche, and the undetected serum androgens levels proves that SF-1 is required for CYP17A1 transcription. The presence of Mullerian structures in case 2 is the most severe reported XY DSD phenotype of *NR5A1* mutation.

REFERENCES

1. Zangen et al. Testicular differentiation factor SF-1 is required for human spleen development. J Clin Invest. 2014 May;124 (5):2071-5.