BROAD RANGE OF PHENOTYPES IN AN INTERNATIONAL COHORT OF 77 DSD INDIVIDUALS WITH SF-1/NR5A1 VARIANTS

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BACKGROUND

Steroidogenic Factor 1 (*NR5A1/SF-1*) is essential for the development and function of human sex and steroid organs. Variants of SF-1 lead to a broad spectrum of phenotypes including adrenal insufficiency and differences of sex development (DSD), but data on the whole picture of phenotypes in individuals with SF-1 variants are currently lacking.

AIM

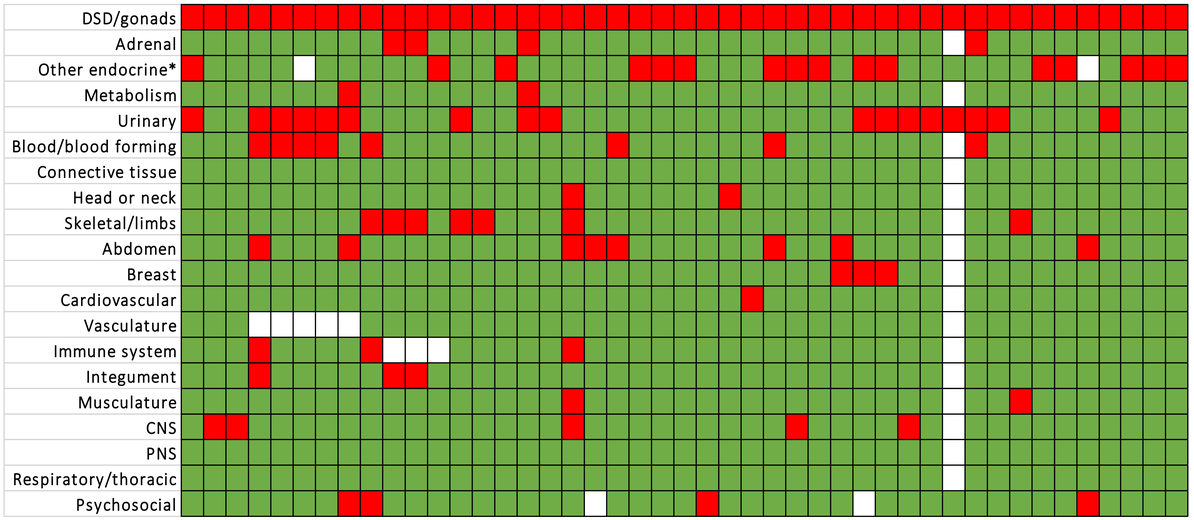
Investigate the phenotype of individuals with SF-1 variants in a large international cohort

METHODS

- Eligible individuals had SF-1 variants and disorders of 46,XX or 46,XY gonadal development, disorders of androgen synthesis/action or non-specific disorders of undervirilization.
- Excluded 46,XX individuals with disorders of androgen excess or disorders of Müllerian development, and 46,XY individuals with Leydig cell defects or Persistent Müllerian Duct Syndrome.
- We identified the individuals through the international I-DSD network.
- Eighteen collaborators entered comprehensive phenotyping data according to the Human Phenotype Ontology project in a RedCap database.

RESULTS

Table: Depicts only 44/77 patients with SF-1/NR5A1 variants who have organ abnormalities apart from DSD, the rest 33 patients with SF-1/*NR5A1* variants have only DSD



Each column represents one patient. Red cells indicate abnormal, green cells normal, and white cells unknown function or morphology.
* Treatment with growth hormone, thyroid hormones or insulin, or abnormal response in HCG or Synacthen (ACTH) stimulation tests

By August 2021, 77 individuals with SF-1 variants participated.

- They were born between 1964-2018 and had their last follow up between 2009-2021.
- Forty-nine percent of individuals were assigned as boys (38/77) and 47% (36/77) as girls. Only 1 % was assigned as "other" (1/77) and 3% had unknown sex assignment (2/77).
- SF-1 variants were mainly identified by single gene analyses (60%, 46/77), followed by gene panels (26%, 20/77), Next Generation Sequencing (13%, 10/77) and Comparative Genomic Hybridization Array (1%, 1/77).
- 44/77 (57%) SF-1 individuals have organ abnormalities (Table)

CONCLUSIONS

More than half of individuals with SF-1 variants had multiple organ abnormalities, with a broad spectrum of phenotypes. Systematic phenotyping together with more comprehensive gene profiling will allow to find patterns in patients with SF-1 variants and to identify likely disease-causing variants in additional genes that might impact the phenotype. Genotype -phenotype patterns will help to evaluate the individual risk for adverse health outcomes and to improve long-term care of individuals with SF-1 variants.

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