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First *NR5A1* Gene Variants in a Cohort of 10 Patients with Disorders of Sex Development in Senegal

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Abstract

Introduction: Sexual differentiation involves numerous genetic factors, including *NR5A1* (Nuclear Receptor Subfamily 5 group A member 1), also known as SF1 (Steroidogenic Factor 1) or A4BP (Adrenal 4 Binding Protein), which is expressed very early in the undifferentiated gonad. Variants of this gene can cause Disorders of Sexual Development (DSD). The aim of this study was to identify variants of the *NR5A1* gene in a cohort of patients with DSD. **Materials and Methods:** Ten patients registered as female at birth were selected from those referred for genetic tests to diagnose a sexual anomaly. After obtaining informed consent, we performed DNA (Deoxyribonucleic Acid) extraction in EDTA tubes, followed by polymerase chain reaction (PCR) amplification and Sanger sequencing of exon 4 of the *NR5A1* gene. **Results:** The entire cohort (100%) presented at least one variant in exon 4 of the *NR5A1* gene. In total, seven (7) different positions within this exon exhibited variants, including the c.437G>C (p.Gly146Ala) variant, which was present in the entire cohort (100%). **Conclusion:** For the first time in Senegal, variants of the *NR5A1* gene have been identified in patients with disorders of sexual development. The c.437G>C (p.Gly146Ala) variant can be found in a variety of phenotypes.

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Keywords

NR5A1, Disorders of Sex Development, Sanger Sequencing, pGly146Ala

1. Introduction

Disorders of Sex Development (DSD) are congenital conditions in which chromosomal, gonadal, and anatomical sex are atypical [1]-[5]. Genetic sex (primary sex differentiation) induces the determination of gonadal sex (ovaries or testes), which itself determines phenotypic sex (secondary sex differentiation), defined by internal genital tracts and external genitalia [6]. During the undifferentiated phase, many genes are expressed in both sexes at a low and similar level [7]-[10]. Thus, they are all necessary for the establishment of the gonad regardless of sex. *NR5A1* (*SF1*, *A4BP*), *WT1* (Wilms Tumor suppressor gene 1), *WNT4* (Wingless-type gene 4) are expressed in the urogenital ridge and play a role in the formation of gonads, kidneys, and adrenal cortex [11]-[16]. *NR5A1*, located at 9q33, encodes the transcription factor steroidogenic factor-1 (SF-1), which is involved in gonad development as well as adrenal gland development [17]. In 2001, De Santa Barbara *et al.* showed that *NR5A1* is expressed in the genital ridge and then in somatic cells of the undifferentiated gonad before *SRY* (*Sex-Determining Region of Y Chromosome*) expression [18]. It has also been shown to participate in the regulation of *SRY* expression during male gonad differentiation. Once the gonad is differentiated, its expression persists in Sertoli cells and Leydig cells during testicular development. *NR5A1* is secondarily involved in the development of the genital tract, as it regulates AMH levels [19] in association with other genes involved in gonad development, such as *WT1* and *SOX9* (*SRY Homebox-Like Gene* 9) [20]. The objective of this study was to search for variants of the *NR5A1* gene in a cohort of patients with disorders of sex development.

2. Materials and Methods

Ten (10) patients were selected from those referred for disorders of sex development (21, 59, 72, 73, 75, 95, 99, 119, AD, AN). In addition, two controls were included in the study: a male control with normal sex differentiation and fertility (T.H) and a female control with normal sex differentiation and fertility (T.F).

After informed consent, we proceeded to collect blood in an EDTA tube for DNA extraction using the "Quick DNA Miniprep" kit protocol. Polymerase chain reaction (PCR) amplification was then performed using specific forward and reverse primers (**Table 1**).

Table 1. *NR5A1* exon 4 primers used.

Gene ***NR5A1***	**Exon**	Primer F	Primer R
	Exon 4	5'-GTG TTG AGC CAG GGG AGA GAG-3'	5'-AGA GAA GGG CTC TGG GTA GC-3'

We focused on exon 4 because, during the period of our study, the majority of variants were listed in this region (Figure 1).

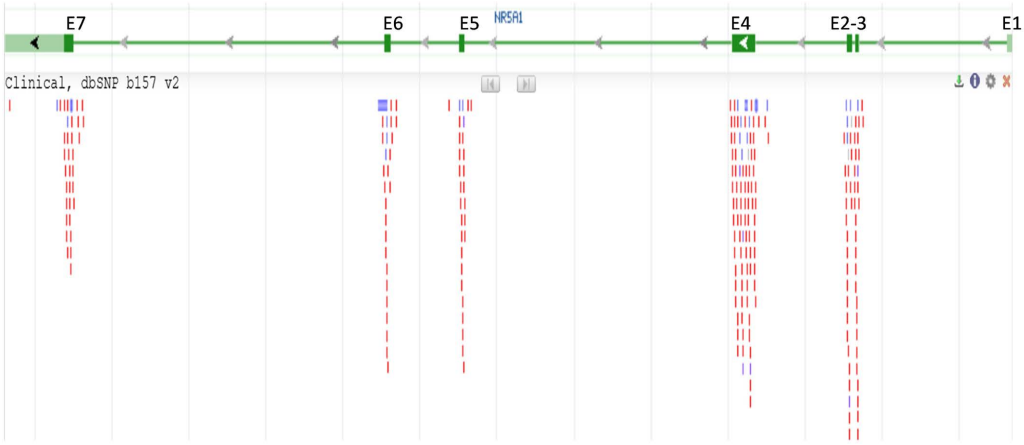

Figure 1. NCBI cited variations on different *NR5A1* exons.

The PCR mix for a sufficient quantity for 25 µL contained: 1 µL of primer (forward + reverse) + 12.5 µL of Master Mix + 9.5 µL of milliQ water + 2 µL of DNA.

The amplification program for the *NR5A1* gene exon 4 was as follows: 95˚C (5 min), 95˚C (30 s), 58˚C (30 sec), 72˚C (1 min), 72˚C (10 min).

The quality of amplification was verified by migration on a 1.5% agarose gel.

The PCR products were then sequenced according to the Sanger method.

The obtained sequences were processed using the following software: Mutation Surveyor, DNA-Baser, Chromaspro, Geneious, Mega X, BioEdit, and Vision Pro. For the search for variants and their pathogenicity, databases such as NCBI, UCSC, HGVS, ClinVar, dbSNP, Ensembl, OMIM, Orphanet, and GeneCards were used.

3. Results

The 10 patients were registered as female in the civil registry.

The age ranged from 4 to 32 years.

Clinical and paraclinical parameters were collected (Table 2).

Table 2. Parameters collected.

Patient Code	Age (Year)	Legal Gender	Examination	Ultrasound/CT-Scan/Hormone	Caryotype/SRY
21	8	F	Virilization of external genitalia	Internal genitalia not found	46,XX
59	23	F	Primary amenorrhea Absence of breast development Virilization of external genitalia	Absence of gonads on pelvic and inguinal ultrasound examination	46,XY SRY(−)
72	32		Congenital adrenal hyperplasia Absence of breast development Primary amenorrhea	Uterine hypoplasia/ Progesterone 27.31 ng/mL Oestradiol 46.0 pg/mL Androstenedione-Delta: 27.45 ng/mL, 95.86 nmol/L	45,X/46,XX

Continued

73	4	F	Virilization of external genitalia	No testes in the pelvis or inguinal canals; No uterus visualized	46,XX
75	20	F	Primary amenorrhea Breast development (Tanner 5) Virilization of external genitalia	Absence of female internal genitalia; Presence of testes	46,XX SRY(+)
95	19	F	Primary amenorrhea Absence of breast development Mayer-rokitansky Syndrome	Absence of internal genitalia	46,XX
99	17	F	Primary amenorrhea Absence of breast development	Ultrasound: Uterine and ovarian hypoplasia. CT scan: Absence of female internal genitalia (uterus and ovaries), no male genitalia	45,X/46,XX
119	22	F	Primary amenorrhea Absence of breast development	Agenesis of internal genitalia	45,X/46,XX
AD	22	F	Amenorrhee primaire Breast development (Tanner 5) Mayer-Rokitansky Syndrome	Uterus absent; Ovaries visible: right 25 × 22, left 32 × 15. Normal appearance	46,XX
AN	25	F	Primary amenorrhea Absence of breast development	Absence of uterus Histology: Ovotestis	SRY(−)

Table 3. *NR5A1* exon 4 variants.

Patient	Variant's Position	Variant Base	HGVS	Number dbSNP	Transcrit	Protein	Type	Pathogenicity
21	g.11829	G>S	NG_008176.1:g.11829G>C	rs2001663795	NM_004959.5c.368G>C	p.Gly123Ala	Missense	Pathogenic: ovarian insufficiency, spermatic failure
	g.11847	C>Y	NG_008176.1:g.11847C>T	rs200749741	NM_004959.4:c.386C>T	p.Pro129leu	Missense	Pathogenic: ovarian insufficiency, spermatic failure
	g.11898	G>C	NG_008176.1:g11898G>C	rs1110061	NM_004959.4:c.437G>C	p.Gly146Ala	Missense	Benign, 46, XY DSD, infertility
	g.11977	C>Y	NG_008176.1:g.11977C>T	rs113506523	NM_004959.5:c.516C>T	p.Ala172Ala	Synonym	Benign, 46, XY DSD, infertility
59	g.11836	G>R	NG_008176.1:g.11836G>A	rs1110062	NM_004959.4:c.375G>A	p.Pro125Pro	Synonym	Benign, 46, XY DSD, infertility
	g.11898	G>C	NG_008176.1:g.11898G>C	rs1110061	NM_004959.4:c.437G>C	p.Gly146Ala	Missense	Benign, 46, XY DSD, infertility
	g.12069	G>R	NG_008176.1:g.12069G>T	rs770165012		p.Ser203Ile	Missense	Not reported
72	g.11898	G>C	NG_008176.1:g.11898G>C	rs1110061	NM_004959.4:c.437G>C	p.Gly146Ala	Missense	Benign, 46, XY DSD, infertility
	g.12055	G>R	NG_008176.1:g.12055G>A	rs142414614	NM_004959.4:c.594G>A	p.Pro198Pro	Synonym	Benign, 46, XY DSD, infertility
73	g.11836	G>R	NG_008176.1:g.11836G>A	rs11160061	NM_004959.4:c.375G>A	p.Pro125Pro	Synonym	Benign, 46, XY DSD, infertility
	g.11898	G>C	NG_008176.1:g.11898G>C	rs1110061	NM_004959.4:c.437G>C	p.Gly146Ala	Missense	Benign, 46, XY DSD, infertility
	g.11977	C>Y	NG_008176.1:g.11977C>T	rs113506523	NM_004959.5:c.516C>T	p.Ala172Ala	Synonym	Benign, 46, XY DSD, infertility
75	g.11898	G>S	NG_008176.1:g.11898G>C	rs1110061	NM_004959.4:c.437G>C	p.Gly123Ala	Synonym	Benign, 46, XY DSD, infertility
95	g.11836	G>R	NG_008176.1:g.11836G>A	rs1110062	NM_004959.4:c.375G>A	p.Pro125Pro	Synonym	Benign, 46, XY DSD, infertility
	g.11898	G>C	NG_008176.1:g.11898G>C	rs1110061	NM_004959.4:c.437G>C	p.Gly146Ala	Missense	Benign, 46, XY DSD, infertility
	g.12069	G>R	NG_008176.1:g.12069G>T	rs1110061		p.Ser203Ile	Missense	Not reported
119	g.11836	G>R	NG_008176.1:g.11836G>A	rs1110062	NM_004959.4:c.375G>A	p.Pro125Pro	Synonyme	Benign, 46, XY DSD, infertility
	g.11977	C>T	NG_008176.1:g11977C>T	rs113506523	NM_004959.4:c.437G>C	p.Ala172Ala	Synonym	Benign, 46, XY DSD, infertility
	g.11898	G>C	NG_008176.1:g.11898G>C	rs1110061	NM_004959.5:c.516C>T	pGly146Ala	Synonym	Benign, 46, XY DSD, infertility
AN	g.11836	G>A	NG_008176.1:g.11836G>A	rs1110062	NM_004959.4:c.375G>A	p.Pro125Pro	Synonym	Benign, 46, XY DSD, infertility
	g.11898	G>C	NG_008176.1:g.11898G>C	rs1110062	NM_004959.4:c.437G>C	p.Pro146Ala	Missense	Benign, 46, XY DSD, infertility
AD	g.11898	G>S	NG_008176.1:g.11898G>C	rs111898	NM_004959.4:c.437G>C	p.Pro146Ala	Missense	Benign, 46, XY DSD, infertility
TH	g.11898	G>C	NG_008176.1:g.11898G>C	rs1110061	NM_004959.4:c.437G>C	pPro146Ala	Missense	Benign, 46, XY DSD, infertility
TF	g.11898	G>S	NG_008176.1:g.11898G>C	rs1110061	NM_004959.4:c.437G>C	p.Gly146Ala	Missense	Benign, 46, XY DSD, infertility

After sequencing of exon 4 of the *NR5A1* gene, the entire cohort (100%) presented at least one variant at this exon 4, including the controls (T.H and T.F). (Table 3).

In total, seven (7) different positions of this exon showed variants, among which the variant c.437G>C (p.Gly146Ala) was shared by the entire cohort (Figure 2).

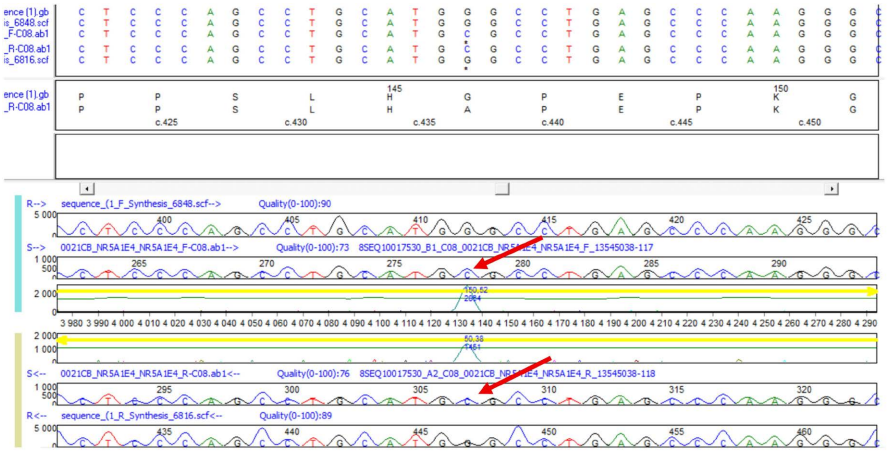

Figure 2. Chromatogram of the variant c.437G>C (p.Gly146Ala).

4. Discussion

NR5A1 variations are among the most frequently identified genetic causes of gonadal development disorders and are associated with a wide phenotypic spectrum [21].

Loss of function of the *NR5A1* gene causes several different phenotypes, including some associated with disease in additional organs [22].

Indeed, all individuals in our cohort presented at least one variant of this gene.

100% of individuals presented the same variant position, g.11898, leading to a change in the produced protein p.Gly146Ala. This variant was also found in controls, raising questions about its pathogenicity.

According to Martinez de Lapiscina*et al.* [23], *NR5A1*/*SF*-1 variants can lead to mild to severe DSD or can be found in healthy carriers (as the controls in our study).

The *NR5A1*/*SF*-1 c.437G>C (p.Gly146Ala) variant is frequent in individuals with DSD and has been suggested to act as a susceptibility factor for adrenal disease [23] (like the patient 72) or cryptorchidism.

At position p11898, two (2) patients (75 and AD) and the female control (TF) were heterozygous, and their phenotype was less ambiguous (breast development stage 5 of Tanner); moreover, these individuals are the only ones to present only one variant on this exon 4. Thus, Martinez de Lapiscina *et al.* state that given the high allele frequency in the general population and the non-conclusive functional tests of the p.Gly146Ala variant, the pathogenic effect of this allele variant has not been judged satisfactory [23].

In addition to the c.437G>C (p.Gly146Ala) variant, 50% of individuals (59, 73, 95, 119, AN) shared another variant position g11836, leading to a synonymous

variant where the produced protein remains Proline (p.Pro125=), however, only patient AN, who was found to have an ovotestis, was homozygous (p.11.836G>A), the others were heterozygous (p.11836G>R).

It would appear that the phenotype varies depending on whether the karyotype is 46,XX or 46,XY. According to Dominice *et al.*, in 46,XY individuals, *NR5A1*-related phenotypes can range from disorders of sex development (DSD) to oligo/azoospermia, and in 46,XX individuals, from 46,XX ovotesticular and testicular DSD to primary ovarian insufficiency (POI) [21]. In an international study in 2024, Kouri *et al.* confirmed the phenotype's diversity among 197 individuals with *NR5A1*/SF-1 variants, and found that over 70% of 46,XY individuals had a severe DSD phenotype, while 90% of 46,XX individuals had female-typical sex development [24].

The most common 46,XY phenotype is the presence of atypical or female external genitalia with clitoromegaly, palpable gonad, and absence of Müllerian derivatives [20]. Notably, undervirilization of external genitalia is frequently observed at birth, while spontaneous virilization may occur later, at puberty: this is the case of patient 59, who has 3 variants observed at different positions compared to the reference genome.

In 46,XX individuals, *NR5A1* mutations are a rare genetic cause of POI, manifesting as primary or secondary amenorrhea, as evidenced by almost the entire cohort (patients 72, 75, 95, 99, 119, AN, AD), infertility, hypoestrogenism, and elevated gonadotropin levels.

Indeed, it is suggested that *NR5A1* gene mutations could be mainly associated with amenorrhea, ovarian failure, hypogonadism, and infertility during puberty [21].

Furthermore, as mentioned earlier, *NR5A1* is involved in the formation of the adrenal gland, and its variants may explain the condition of patient 72, who has been experiencing congenital adrenal hyperplasia since birth and carries a specific variant in the cohort (g.12055G>R). This variant is synonymous with p.Pro198=, considered benign or potentially causing 46,XY or infertility in ClinVar. Patient 21, who had a naked glans surrounded by asymmetric labioscrotal structures and hypospadias, is the only one to have 4 variants on this exon, she carries an isolated variant (g.11847C>Y) which the homozugous form can lead to a missense variant (p.Pro129Leu), and reported as a cause of primary ovarian insufficiency (POI) or infertility in clinVar. She also carries another variant at position g.11977C>Y, leading to a synonymous variant (p.Ala172Ala), which she shared with the patient 73, who had a similar phenotype, and patient 119.

Thus, as our results demonstrate and Faienza *et al.* [25] affirm, the data confirm that *NR5A1* gene mutations can present variable genital phenotypes. Regardless, the reproductive function has always been altered.

According to Luppino *et al.*, Clinical phenotypes may vary, even among patients carrying the same *NR5A1* variant, indicating that there is no specific genotype-phenotype correlation [22].

Naamneh Elzenaty *et al.* hypothesized that the broad phenotype of DSD asso-

ciated with *NR5A1*/SF-1 variants may be caused by an oligogenic mechanism [26].

The observed phenotypic variability in individuals and families with *NR5A1*/SF-1 variants is large and remains unpredictable. It may often not be solely explained by the monogenic pathogenicity of the *NR5A1*/SF-1 variants but is likely influenced by additional genetic variants and as yet unknown factors.

5. Conclusion

Our study is the first in our sub-region to investigate *NR5A1* gene mutations in patients with disorders of sex development. This gene is involved early in sex differentiation, and its variants can explain these conditions. In this study, we focused on exon 4, which suggests the most pathogenic variants, and found 7 different variant positions. As suggested by our patients' conditions, *NR5A1* gene mutations can present variable genital phenotypes.

Ethical Statement

This study was approved by the Doctoral School of Sciences of Life, Health, and Environment (ED/SEV) of Cheikh Anta Diop University and was conducted as part of a Ph.D. thesis (No. 202348, 2023). All procedures were conducted in accordance with the Declaration of Helsinki and adhered to national and institutional ethical guidelines. Written informed consent was obtained from all participants (regarding minors, parental consent was required) after a detailed explanation of the study objectives, procedures, and potential risks.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Lee, P.A., Houk, C.P., Ahmed, S.F. and Hughes, I.A. (2006) https://doi.org/10.1542/peds.2006-0738

[2] Houk, C.P. and Lee, P.A. (2008) Consensus Statement on Terminology and Management: Disorders of Sex Development. *Sexual Development*, **2**, 172-180. https://doi.org/10.1159/000152032

[3] Öçal, G. (2011) Current Concepts in Disorders of Sexual Development. *Journal of Clinical Research in Pediatric Endocrinology*, **3**, 105-114. https://doi.org/10.4274/jcrpe.v3i3.22

[4] Dreger, A.D., Chase, C., Sousa, A., Gruppuso, P.A. and Frader, J. (2005) https://www.degruyterbrill.com/document/doi/10.1515/JPEM.2005.18.8.729/html

[5] Hughes, I.A. (2008) Disorders of Sex Development: A New Definition and Classification. *Best Practice & Research Clinical Endocrinology & Metabolism*, **22**, 119-134. https://doi.org/10.1016/j.beem.2007.11.001

[6] Blecher, S.R. and Erickson, R.P. (2007) Genetics of Sexual Development: A New Paradigm. *American Journal of Medical Genetics Part A*, **143**, 3054-3068. https://doi.org/10.1002/ajmg.a.32037

[7] Ono, M. and Harley, V.R. (2012) Disorders of Sex Development: New Genes, New

Concepts. *Nature Reviews Endocrinology*, **9**, 79-91.
https://doi.org/10.1038/nrendo.2012.235

[8] MacLaughlin, D.T. and Donahoe, P.K. (2004) Sex Determination and Differentiation. *New England Journal of Medicine*, **350**, 367-378.
https://doi.org/10.1056/nejmra022784

[9] Brennan, J. and Capel, B. (2004) One Tissue, Two Fates: Molecular Genetic Events That Underlie Testis versus Ovary Development. *Nature Reviews Genetics*, **5**, 509-521. https://doi.org/10.1038/nrg1381

[10] Biason-Lauber, A. (2010) Control of Sex Development. *Best Practice & Research Clinical Endocrinology & Metabolism*, **24**, 163-186.
https://doi.org/10.1016/j.beem.2009.12.002

[11] Çetinkaya, E., Öcal, G., Berberoğlu, M., Adiyaman, P., Ekim, M., Yalçinkaya, F., *et al.* (2001) Association of Partial Gonadal Dysgenesis, Nephropathy and *WT1* Gene Mutation without Wilms' Tumor: Incomplete Denys-Drash Syndrome. *Journal of Pediatric Endocrinology and Metabolism*, **14**, 561-564.
https://doi.org/10.1515/jpem.2001.14.5.561

[12] Wilhelm, D. and Englert, C. (2002) The Wilms Tumor Suppressor *WT1* Regulates Early Gonad Development by Activation of *Sf1*. *Genes & Development*, **16**, 1839-1851.
https://doi.org/10.1101/gad.220102

[13] Sekido, R. and Lovell-Badge, R. (2008) Sex Determination Involves Synergistic Action of SRY and SF1 on a Specific *Sox9* Enhancer. *Nature*, **453**, 930-934.
https://doi.org/10.1038/nature06944

[14] Zhao, L., Bakke, M., Krimkevich, Y., Cushman, L.J., Parlow, A.F., Camper, S.A., *et al.* (2001) Steroidogenic Factor 1 (SF1) Is Essential for Pituitary Gonadotrope Function. *Development*, **128**, 147-154. https://doi.org/10.1242/dev.128.2.147

[15] Huguet, E.L., McMahon, J.A., McMahon, A.P., Bicknell, R. and Harris, A.L. (1994) Differential Expression of Human Wnt Genes 2, 3, 4, and 7B in Human Breast Cell Lines and Normal and Disease States of Human Breast Tissue. *Cancer Research*, **54**, 2615-2621.

[16] Biason-Lauber, A., Konrad, D., Navratil, F. and Schoenle, E.J. (2004) A *wnt*4 Mutation Associated with Müllerian-Duct Regression and Virilization in a 46,XX Woman. *New England Journal of Medicine*, **351**, 792-798. https://doi.org/10.1056/nejmoa040533

[17] Val, P. and Swain, A. (2010) Gene Dosage Effects and Transcriptional Regulation of Early Mammalian Adrenal Cortex Development. *Molecular and Cellular Endocrinology*, **323**, 105-114. https://doi.org/10.1016/j.mce.2009.12.010

[18] de Santa Barbara, P., Méjean, C., Moniot, B., Malclès, M., Berta, P. and Boizet-Bonhoure, B. (2001) Steroidogenic Factor-1 Contributes to the Cyclic-Adenosine Monophosphate Down-Regulation of Human SRY Gene Expression. *Biology of Reproduction*, **64**, 775-783. https://doi.org/10.1095/biolreprod64.3.775

[19] Arango, N.A., Lovell-Badge, R. and Behringer, R.R. (1999) Targeted Mutagenesis of the Endogenous Mouse Mis Gene Promoter. *Cell*, **99**, 409-419.
https://doi.org/10.1016/s0092-8674(00)81527-5

[20] Burris, T.P., Guo, W.W., Le, T. and Mccabe, E.R.B. (1995) Identification of a Putative Steroidogenic Factor-1 Response Element in the DAX-1 Promoter. *Biochemical and Biophysical Research Communications*, **214**, 576-581.
https://doi.org/10.1006/bbrc.1995.2324

[21] Domenice, S., Machado, A.Z., Ferreira, F.M., Ferraz-de-Souza, B., Lerario, A.M., Lin, L., *et al.* (2016) Wide Spectrum of *NR5A1*-Related Phenotypes in 46,XY and 46,XX Individuals. *Birth Defects Research Part C*: *Embryo Today*: *Reviews*, **108**, 309-320.

https://doi.org/10.1002/bdrc.21145

[22] Luppino, G., Wasniewska, M., Coco, R., Pepe, G., Morabito, L.A., Li Pomi, A., *et al.* (2024) Role of *NR5A1* Gene Mutations in Disorders of Sex Development: Molecular and Clinical Features. *Current Issues in Molecular Biology*, **46**, 4519-4532. https://doi.org/10.3390/cimb46050274

[23] Martinez de Lapiscina, I., Kouri, C., Aurrekoetxea, J., Sanchez, M., Naamneh Elzenaty, R., Sauter, K., *et al.* (2023) Genetic Reanalysis of Patients with a Difference of Sex Development Carrying the *NR5A1*/*SF-1* Variant p.Gly146Ala Has Discovered Other Likely Disease-Causing Variations. *PLOS ONE*, **18**, e0287515. https://doi.org/10.1371/journal.pone.0287515

[24] Kouri, C., Sommer, G., Martinez De Lapiscina, I., Elzenaty, R.N., Tack, L.J.W., *et al.* Clinical and Genetic Characteristics of a Large International Cohort Individuals with Rare *NR5A1*/SF-1 Variants of Sex Development. *eBioMedecine*, **99**, 1-16.

[25] Faienza, M.F., Chiarito, M., Baldinotti, F., Canale, D., Savino, C., Paradies, G., *et al.* (2019) *NR5A1* Gene Variants: Variable Phenotypes, New Variants, Different Outcomes. *Sexual Development*, **13**, 258-263. https://doi.org/10.1159/000507411

[26] Naamneh Elzenaty, R., Martinez de Lapiscina, I., Kouri, C., Sauter, K., Sommer, G., Castaño, L., *et al.* (2024) Characterization of 35 Novel *NR5A1*/SF-1 Variants Identified in Individuals with Atypical Sexual Development: The SF1 Next Study. *The Journal of Clinical Endocrinology & Metabolism*, **110**, e675-e693. https://doi.org/10.1210/clinem/dgae251