

## Gene Section

### Review

# NR5A1 (nuclear receptor subfamily 5, group A, member 1)

Carmen Ruggiero, Mabrouka Doghman, Enzo Lalli

Institut de Pharmacologie Moleculaire et Cellulaire CNRS, Valbonne 06560, France (CR), Associated International Laboratory (LIA) NEOGENEX CNRS, Valbonne 06560, France (MD), University of Nice-Sophia-Antipolis, Valbonne 06560, France (EL)

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## Abstract

Review on NR5A1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

## Identity

**Other names:** AD4BP, ELP, FTZ1, FTZF1, POF7, SF-1, SF1, SPGF8, SRXY3

**HGNC (Hugo):** NR5A1

**Location:** 9q33.3

**Note:** Steroidogenic factor-1 (SF-1) is an orphan member of the nuclear receptor superfamily which acts as a key regulator of adrenogonadal development and tissue-specific gene expression in steroidogenic cells. Parker's and Morohashi's groups identified SF-1 by its capacity to activate transcription from multiple P450 steroidogenic enzyme promoters (Lala et al., 1992; Morohashi et al., 1992). Besides its recognized role as a master regulator of steroidogenesis in the adrenal cortex and gonads, recent studies indicate that the regulation of gene expression in the adrenal cortex by SF-1 also involves processes other than steroidogenesis (reviewed in Lalli et al., 2013).

## DNA/RNA

In 1992 the mouse Sf-1 gene (Nr5a1) was cloned from an adrenal cDNA library using a probe corresponding to the DNA-binding domain (DBD) of the related orphan receptor retinoid X receptor (Lala et al., 1992).

Later, its bovine homologue (called adrenal 4-binding protein, Ad4BP) was identified from an adrenal cDNA library exploiting the partial sequence of a protein purified from bovine adrenal extracts (Honda et al., 1993). The proteins encoded by both these murine and bovine cDNAs were able to activate promoters of steroid hydroxylase enzymes, indicating that a common steroidogenic factor had been identified. Initially the mouse gene encoding SF-1 was called Ftzf1, similar to the *Drosophila* orphan nuclear receptor fushi tarazu factor homolog 1 (FTZ-F1) and mapped to chromosome 2 (Ueda et al., 1990; Swift and Ashworth, 1995; Taketo et al., 1995).

The corresponding human SF-1 gene was initially termed FTZF1 and later NR5A1 (see above) according to the standard nomenclature system for nuclear receptors.

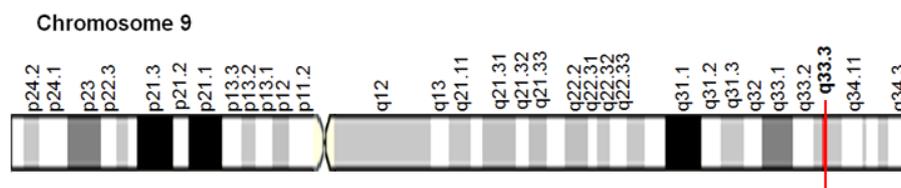


Figure 1. NR5A1 chromosomal localization. The NR5A1 gene maps on chromosome 9q33.3 (adapted from GeneCards).



**Figure 2. Structure of the SF-1 protein.** SF-1 contains the major structural features present in all nuclear receptors. N, N-terminus of the protein; DBD, DNA binding domain with two zinc finger (ZnI and ZnII) motifs; Ftz-F1, Fushi-tarazu-F1 domain with a nuclear localization signal (NLS); Hinge, hinge region displaying a Pro-rich (proline-rich) region and an AF-1- (transcriptional activation domain 1) like domain; LBD, ligand-binding domain; AF-2, transcriptional activation domain 2; C, C-terminus of the protein.

### Description

Size: 26.18 Kb (GeneCards), 7 exons. mRNA: 3095 bp (NM\_004959).

### Transcription

The human NR5A1 gene is mapped to the long arm of chromosome 9 (9q33, Figure 1) and consists of 7 exons spanning approximately 27 Kb of genomic DNA (Taketo et al., 1995; Oba et al., 1996; Wong et al., 1996). Exon 1 is untranslated.

## Protein

### Description

The SF-1 protein contains the typical domains of other members of the nuclear receptor superfamily (NURSA): an N-terminal DBD including two zinc fingers, a flexible proline-rich hinge region displaying AF-1 - like activation activity, a ligand binding domain (LBD) and a C-terminal AF-2 activation domain, which is required for transcriptional activity and cofactor interactions (Figure 2).

A proximal (P) box implicated in the specific recognition of DNA target sequences by nuclear receptors has been described in the first zinc finger of SF-1 DBD. This sequence interacts with the hormone response element core in the major groove of the DNA helix by recognizing variations on the AGGTCA motif (Evans, 1998). SF-1 also exhibits a FTZ-F1 box or A box, which represents a 30-aminoacid extension of the DBD, being important for DNA anchoring. Indeed, at variance from most nuclear receptors, SF-1 binds to target genes monomerically rather than as a homo- or heterodimer and with highest affinity to 5'YCAAGGYCR'3 (where Y= T/C; R= G/A) (Ueda and Hirose, 1991; Wilson et al., 1993). X-ray crystallography of the SF-1 DBD complexed with a sequence in the inhibin- $\alpha$  gene proximal promoter region has shown that the A-box primarily interacts with the 5' flanking sequence and the first part of the half site in the minor groove of DNA (Ito et al., 2000a; Little et al., 2006). Moreover, the same study revealed that SF-1 displays a helix in the C-terminal segment of the FTZ-F1 box which interacts with both the core DBD and the DNA, thus acting as an important determinant of the complex stability (Little et al., 2006). It has been proposed that this

helix may also serve as a platform for coactivators and other DNA-bound factors interaction (Little et al., 2006).

The hinge region, which lies between the N-terminal DBD and the C-terminal LBD is more than a flexible connector between the LBD and the DBD. It participates in conjunction with helix 1 (H1, see below) to promote an active protein conformation (Desclozeaux et al., 2002). Furthermore, it is important for post-transcriptional/translational modifications, like phosphorylation and SUMOylation (Hammer et al., 1999; Komatsu et al., 2004; Lee et al., 2005; Lewis et al., 2008). In particular, phosphorylation of the hinge region enhances SF-1 overall stability and transcriptional activity (Desclozeaux et al., 2002).

The LBD contains 12 helices (H1-H12, like other nuclear receptors), that can form an AF2 domain for the recruitment of cofactors. SF-1 has been considered as an "orphan" nuclear receptor for many years because of the absence of high-affinity naturally occurring ligands identified. This led to the hypothesis that the LBD of SF-1 could adopt a stable conformation in the absence of ligand (Desclozeaux et al., 2002). Later, different groups have been able to crystallize the SF-1 LBD, showing that small phospholipids ligands (e.g. phosphatidylinositols) can bind to this domain (Krylova et al., 2005; Li et al., 2005; Wang et al., 2005).

Protein translation:

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MDYSYDEDLD ELCPCVCGDKV SGYHYGLLTC
ESCKGFFKRT VQNNKHYTCT ESQSCKIDKT
QRKRCPCFRF QKCLTVGMRL
EAVRADRMRG GRNKFGPMYK
RDRALKQKK AQIRANGFKL ETGPPMGVPP
PPPPAPDYVL PPSLHGPEPK GLAAGPPAGP
LGDFGAPALP MAVPGAHGPL AGYLYPAFFG
RAIKSEYPEP YASPPQGPL YGYPEPFSGG
PNVPELILQL LQLEPDEDQV RARILGCLQE
PTKSRPDQPA AFGLLCRMAD QTFISVDWA
RRCMVFKELE VADQMTLLQN
CWSELLVFDH IYRQVQHGKE GSILLVTGQE
VELTTVATQA GSLHSLVLR AQELVLQLLA
LQLDRQEFVC LKFIILFSLD LKFLNNHILV
KDAQEKANAA LLDYTLCHYP
HCGDKFQQLL LCLVEVRALS
MQAKEYLYHK HLGNEPRNN
LLIEMLQAKQ T
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Sequence length: 461 aa; Molecular weight: 51,636 kDa

### **Expression**

SF-1 localization in adult tissues has been widely investigated in mice, rats, human and other vertebrates. Its expression pattern is consistent with its role as a steroidogenesis master regulator and is strikingly overlapping with that of another nuclear receptor, Dax-1 (Nr0b1) (Ikeda et al., 1996; Swain et al., 1996; Tamai et al., 1996; Ikeda et al., 2001), which functions as a negative regulator of SF-1 activity. SF-1 is expressed in tissues involved in steroid hormone production and reproductive function, i.e. the three layers of the adrenal cortex, testicular Leydig and Sertoli cells, ovarian interstitium, theca and granulosa cells, and, to a lesser degree, corpus luteum (Honda et al., 1993; Ikeda et al., 1993; Morohashi et al., 1994; Ramayya et al., 1997; Morohashi, 1999). SF-1 is also expressed in non-steroidogenic tissues like pituitary gonadotropes. It is also expressed in the dorsomedial portion of the ventromedial hypothalamus (VMH) (Ikeda et al., 1994; Shinoda et al., 1995), in the endothelial linings of the venous sinuses and pulp veins in the spleen (Ramayya et al., 1997; Morohashi et al., 1999), and in a subset of hippocampal neurons. It has been described that in developing human embryos SF-1 represents the earliest marker of adrenogonadal differentiation, first appearing in the urogenital ridge (Ikeda et al., 1994; Morohashi et al., 1995; Hanley et al., 1999; Hanley et al., 2001).

In the mouse, SF-1 is first expressed at embryonic day 9 (E9.0) in the adrenal/gonadal primordium (AGP) (Hatano et al., 1996). After gonadal and adrenal anlagen separation at E11.0, SF-1 is expressed throughout gestation in the developing steroidogenic adrenal portion and in zona glomerulosa, fasciculata and reticularis of the adult gland. In contrast, it is not expressed in the neural crest cells that migrate to the medulla during development (Ikeda et al., 1994) nor in the adult medulla (Ikeda et al., 1993). While SF-1 is expressed in the indifferent gonad, it displays a sexually dimorphic expression pattern in the developing testis and ovaries (Ikeda et al., 1994). Indeed, it disappears from the ovaries between E13.5 to E16.5 and reappears at the beginning of folliculogenesis, being expressed in granulosa, thecal and luteal cells of the adult ovary (see above, Ikeda et al., 1993; Hanley et al., 1999; Hanley et al., 2001).

During embryonic development, SF-1 expression is tightly temporally and spatially controlled. An E-box-binding site within the basal promoter of SF-1 gene has been described to be critical for SF-1 expression (Nomura et al., 1995). The transcription factor POD1/capsulin has been reported to repress SF-1 expression in the gonad through binding to this E-box (Tamura et al., 2001; Cui et al., 2004),

whereas WT1 plays a role as a positive regulator of SF-1 expression in the developing gonad (Wilhelm and Englert, 2002), like the LIM homeobox gene Lhx9 (Birk et al., 2000). Interestingly, genetic and molecular evidence shows that the transcription co-factor CITED2 interacts with WT1 to promote SF-1 expression in the AGP before the separation between gonad and adrenal cortex, a critical time during embryogenesis (Val et al., 2007).

Recently, Morohashi and collaborators have identified one intergenic and three intragenic (intronic) enhancers, which are essential for tissue and SF-1 stage specific expression in mice. Those tissue-specific enhancers direct SF-1 expression to the fetal adrenal (Fetal Adrenal Enhancer, fAdE, localized to intron 4) (Zubair et al., 2006), the developing pituitary and adult gonadotropes (Pituitary Gonadotrope Enhancer, PGE, localized to intron 6) (Shima et al., 2008), the developing diencephalon and adult VMH (VMH Enhancer, VMHE, localized to intron 6, upstream of PGE) (Shima et al., 2005) and fetal Leydig cells (Fetal Leydig cell Enhancer, FLE; intergenic, located upstream of the transcriptional start site) (Shima et al., 2012). Although the activity of these enhancers has been established only in mice, all enhancers, like the basal promoter, are conserved among the different animal species (Shima et al., 2012).

### **Localisation**

SF-1 is constitutively localized in the nucleus where it acts as a DNA-binding transcription factor. Interestingly, it has been described that it also moves inside the nucleus according to the status of its post-translational modifications (Chen et al., 2004; Fan et al., 2004). SUMOylation seems to repress SF-1 activity as the mutations of its SUMO acceptor sites K119 and K194 enhance SF-1 - driven gene activation. It has been proposed that SUMO-conjugated SF-1 localizes to the PML nuclear speckles, where SF-1 is sequestered from nucleoplasm and is associated with repressors, like DP103 (Lee et al., 2005; Wang et al., 2013). SF-1 can also be acetylated at the KQQKK sequence in the Ftz-F1 box and activated by the histone acetyltransferase p300 (Chen et al., 2005). Following cAMP stimulation, SF-1 spreads out into discrete transcriptionally active foci containing RNA polymerase II, p300 (Chen et al., 2005) and the ubiquitous histone acetyltransferase GCN5 (Fan et al., 2004). It has been hypothesised that SF-1 is recruited to those transcriptionally active loci as a result of physical interactions with co-regulators like p300 and GCN5. Furthermore, when SF-1 is acetylated by p300 at the FTZ-F1 domain, its binding to p300 increases. It seems that acetylation is involved in retaining SF-1 in the transcriptionally active nuclear foci, thus promoting SF-1 - mediated target gene transcription (Chen et al., 2005). Neither

phosphorylation at Ser 203 (Hammer et al., 1999) nor ubiquitination (Chen et al., 2007) appear to change or affect SF-1 distribution. Recently, it has been shown that SF-1 is also located in the centrosome. Immunofluorescence analysis revealed that it colocalizes with the centrosome marker  $\gamma$ -tubulin in mouse adrenocortical Y1 and mouse testicular Leydig MA-10 cells (Lai et al., 2011). Sucrose gradient fractionation studies in Y1 cells have confirmed immunofluorescence results (Lai et al., 2011). A centrosome localization signal (CLS) has also been identified by deletion analysis and localized to aa 348-367 (Lai et al., 2011). Moreover, SF-1 centrosomal localization results to be independent from microtubule (MT) transportation, as after MT depolymerization SF-1 still colocalizes with acetylated tubulin (Wang et al., 2013).

## Function

### SF-1 as a master regulator of gene expression in steroidogenic cells

SF-1 was identified as a key factor that regulates the expression of several steroidogenic enzymes in a tissue-specific manner (Lala et al., 1992; Morohashi et al., 1992). In steroidogenic tissues, SF-1 regulates steroidogenic pathways including genes encoding cytochrome P450 enzymes as CYP11A1 (Chau et al., 1997), CYP17A1 (Bakke et al., 1995), CYP21A2, CYP11B1 (Morohashi et al., 1993), CYP11B2 (Bassett et al., 2002),  $3\beta$ -hydroxysteroid dehydrogenase ( $3\beta$ HSD) (Leers-Sucheta et al., 1997), steroidogenic acute regulatory protein (StAR) (Sugawara et al., 1996). Other evidence shows that SF-1 regulates many genes involved in development and steroidogenic function (reviewed in Schimmer and White, 2010). SF-1 is generally considered as an activator of gene expression, but it can act as a negative regulator of the type 4 adenylyl cyclase and of CYP11B2 (Rui et al., 2008; Ye et al., 2009). SF-1 also regulates genes involved in sex determination and development of reproductive tissues including DAX1, AMH, SOX9, SRY (Kawabe et al., 1999; De Santa Barbara et al., 1998; De Santa Barbara et al., 2001; Sekido et al., 2008). Thus, SF-1 plays a central role in development and function of the steroidogenic and reproductive systems.

Some SF-1-interacting proteins (positive and negative cofactors) are expressed in a tissue-specific manner whereas others are more widely expressed. Further studies are necessary to better understand how these cofactors could contribute to control cell- and time-specific expression of SF-1-dependent genes. Interactions between SF-1 and DAX-1 represent a particular interest (Ikeda et al., 1996). DAX1, an X-linked gene that encodes a repressor of steroidogenic gene expression, modulates the activity of SF-1 (Lalli et al., 1998). Mutations in DAX-1 cause X-linked adrenal hypoplasia congenita and hypogonadotropic hypogonadism, phenotypes

similar to those seen with NR5A1 mutations (reviewed in Lalli, 2003 and Lalli, 2014).

Putative phospholipid ligands, post-translational modifications (phosphorylation, sumoylation, acetylation), epigenetic gene expression regulation and gene dosage (see below) can influence SF-1 transcriptional activity, subnuclear localization and/or DNA-binding activity (reviewed in Hoivik et al., 2010; Lalli, 2010; Schimmer and White, 2010). By different genomic approaches, multiple levels of regulation exerted by SF-1 dosage on transcriptome, and more recently on its cistrome have been explored (Doghman et al., 2007; Doghman et al., 2013). These recent studies have shown that SF-1 regulates distinct categories of genes in adrenocortical cancer cells according to its dosage. Moreover, the binding of SF-1 to chromatin sites in condition of different SF-1 dosage correlates with differential regulation of gene expression (Doghman et al., 2013). Transcriptional profiling revealed that SF-1 dosage-dependent genes are involved in lipid and steroid metabolism, but also in apoptosis, cell cycle regulation, cell adhesion and transcriptional regulation (reviewed in Lalli et al., 2013). Other recent studies show that SF-1 knockdown affects the expression of a large number of transcripts that are not only involved in steroid synthesis (Schimmer et al., 2011). A recent study suggested that SF-1 may be involved in glucose metabolism by regulating genes of the glycolytic pathways (Baba et al., 2014) even if this was not observed in other studies (Schimmer et al., 2011; Doghman et al., 2013).

### From Knock-out mice models to human mutations phenotype: Evidence of the key role of SF-1 in differentiation and development.

Studies of both complete and tissue-specific knockout mice have demonstrated that SF-1 is a key factor for the development of the adrenal glands, gonads, ventromedial hypothalamus and in pituitary gonadotropes functions (Luo et al., 1994; Sadovsky et al., 1995; Shinoda et al., 1995; Ikeda et al., 1995; Zhao et al., 2001). To characterize the role of SF-1 in different tissues and to distinguish between the direct and secondary effects of SF-1 deficiency, Keith Parker's laboratory developed mice models that are specifically deleted for Sf-1 in gonadotrope cells, gonads and VMH by using the Cre/lox approach (Jeyasuria et al., 2004; Pelusi et al., 2008; Zhao et al., 2008).

### Role in adrenal and gonads

Sf-1 null mice lack adrenal glands and gonads and die from adrenal insufficiency within the first week after birth. Mice lacking Sf-1 show early adrenal and gonadal development that regresses by apoptosis between E11.5 and E12.5 (Luo et al., 1994; Sadovsky et al., 1995) indicating that Sf-1 is essential for early development and maintenance of adrenal and gonadal primordia.

SF-1 knockout mice exhibited male-to-female sex reversal of their internal and external genitalia. Since their gonads regressed before male sexual differentiation normally occurs, the internal and external urogenital tracts of SF-1 KO mice are female irrespective of genetic sex. Absence of testes in homozygous mutant male mice precludes MIS (Müllerian inhibiting substance) and androgen production, which accounts for the observed phenotypes (Luo et al., 1994; Sadovsky et al., 1995). Heterozygous Sf-1 null mice have decreased adrenal volume associated with impaired corticosterone production in response to stress and present smaller testes (Bland et al., 2000). These mice also present a defect in compensatory growth in the remaining adrenal following unilateral adrenalectomy, indicating that SF-1 is required for cell proliferation in steroidogenic tissue (Beuschlein et al., 2002). Differences in adrenal development between heterozygous animals and their wild-type littermates were more evident during embryonic development than postnatally due to a partial compensation of adrenal function after birth (Bland et al., 2004). Thus, a difference between the capacity of the adrenal gland and gonad to compensate for partial loss of SF-1 function might be one of the mechanisms explaining why the gonadal phenotype is more marked than the adrenal phenotype in humans with heterozygous NR5A1 mutations (see Implications in pathology).

Male gonad-specific Sf-1 KO mice display hypoplastic testes observed starting from early developmental stages associated with an impaired spermatogenesis which makes the animals sterile. Moreover, in this model, the testes do not descend (cryptorchidism), demonstrating an *in vivo* important role of SF-1 in hormonal production for virilization and testes descent (Jeyasuria et al., 2004). SF-1 KO ovaries were indistinguishable from wild-type during embryogenesis and at birth, but adult females were sterile. In the ovaries, the total number of ovarian follicles is decreased and corpora lutea are lacking, indicating an important role for SF-1 in ovulation (Jeyasuria et al., 2004). SF-1 is then essential for normal gonadal function in both male and female mice.

#### **Role in anterior pituitary, VMH and spleen**

The consequences of SF-1 KO at the level of pituitary and hypothalamus have important impacts on their target organs. Indeed, the pituitaries of SF1 knockout mice have markedly decreased expression of both pituitary gonadotropins [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] and have impaired expression of many target genes that regulate gonadal steroidogenesis (Ingraham et al., 1994; Shinoda et al., 1995). However, GnRH treatment of SF-1 knockout mice induced pituitary expression of LH and FSH, indicating that

gonadotropes can express putative SF-1 target genes in the absence of SF-1 (Ikeda et al., 1995).

The pituitary-specific Sf-1 KO mice have markedly decreased levels of LH and FSH and exhibit hypoplastic gonads, impaired secondary sexual development and are sterile. Administration of gonadotropins partially rescues the gonadal phenotype. All these studies establish a primary role for SF-1 in gonadotrope function in the pituitary in mice (Zhao et al., 2001).

In the brain of SF-1 KO mice, the region of the ventromedial hypothalamus is disorganized and does not show its characteristic structures. The VMH is a hypothalamic region linked to feeding and appetite regulation and female reproductive behavior (Shinoda et al., 1995; Ikeda et al., 1995; Zhao et al., 2001). SF-1 is the only gene that is specifically and exclusively expressed in the VMH. It is noteworthy that SF-1 KO mice that are maintained alive by adrenal transplantation exhibit late onset obesity suggesting a potential role of SF-1 in regulation of food intake (Majdic et al., 2002).

The nestin promoter, which is active in the CNS, was used to create a brain-specific Sf-1 KO mice<sup>nCre; F/-</sup> model equivalent of a VMH-specific knockout (Zhao et al., 2008). The organization of VMH neurons is dramatically changed in this model, and mice also present an increased anxiety-like behavior and a decreased locomotor activity (Zhao et al., 2008). Moreover, Sf-1 KO<sup>nCre; F/-</sup> female mice have impaired follicle development, fertility and sexual behaviors and normal body weight, delineating an important role for SF-1 expressed in the VMH in female reproductive function, independently of energy balance regulation (Kim et al., 2010). To distinguish between the direct metabolic roles of SF-1 and its developmental side effects, an alternative mouse model named postnatal VMH-specific SF-1 KO was generated in which SF-1 is specifically deleted after completion of VMH development using CamKII-Cre, a postnatally expressing Cre line (Kim et al., 2011). These postnatal VMH-specific Sf-1 KO animals display a diet-induced obesity and revealed that SF-1 is required for normal energy homeostasis by modulating energy expenditure especially in high-fat diet condition (Kim et al., 2010). Although SF-1-expressing neurons do not represent all neurons within the VMH, many studies establish that SF-1 neurons in the VMH are essential for normal energy homeostasis, particularly in regulation of energy expenditure (reviewed in Choi et al., 2013).

It has been shown that disruption of SF-1 also causes developmental abnormalities in spleen tubular structure and impaired clearance by the splenic vascular system (Morohashi et al., 1999). Similar defects have been observed in mice with disruption of the mouse polycomb 33 gene (M33) and suggest

an interaction between M33 and SF-1 in splenic development (Katoh-Fukui et al., 2005).

#### **SF-1 involvement in human disease**

Genetic evidence for the essential role of SF-1 in endocrine development also comes from studies on human patients. These genetic mutations provide insights into the function of SF-1 and the mechanisms of XY sex reversal, ovarian anomalies and adrenal failure (reviewed in Lin and Achermann, 2008).

More than 70 human SF-1 mutations have been described, with most of them found in a heterozygous state and only a few found in homozygote or compound heterozygote state (see Mutation). In humans, the first description of a heterozygous loss-of-function SF-1 mutation (G35E) was made in a patient with adrenal failure and complete 46,XY sex-reversal, closely matching the phenotype of Sf-1 null mice (Achermann et al., 1999). Afterwards, several other patients have been described presenting variable degrees of gonadal and adrenal dysgenesis caused by SF-1 haploinsufficiency, while only one homozygous SF-1 mutation has been described (R92Q) in a patient with adrenal hypoplasia and 46,XY sex-reversal (Achermann et al., 2002). In several cases, SF-1 haploinsufficiency has been shown to be associated with isolated gonadal dysgenesis or ovarian insufficiency, while only one case has been described of a prepubertal girl with adrenal insufficiency and apparently normal ovaries (Biaison-Lauber et al., 2000). It appears that a species difference exists in the sensitivity to SF-1 dosage. In fact, while adrenals and gonads are both affected by Sf-1 haploinsufficiency in mice, in humans the great majority of heterozygote SF-1 mutations are associated with disorders of sex development (Lin et al., 2007), premature ovarian failure (Lourenço et al., 2009) or male infertility (Bashamboo et al., 2010) rather than adrenal development (see Mutation and Implication in pathology).

Recently, novel SF-1 mutations were identified in patients with 46,XY DSD and adrenal insufficiency. In vitro analysis revealed that these SF-1 mutations affect not only steroidogenesis but also transcription of the BDNF gene that is involved in energy balance (Malikova et al., 2014). However, in contrast to mice, consequences on weight were not found in humans with SF-1 mutations and further studies are necessary to confirm the impact of SF-1 on body weight regulation in human.

A recent study describes a clinical phenotype of severe 46,XY-DSD with asplenia, caused by a novel homozygous SF1 mutation (R103Q) suggesting that SF-1 is required for spleen development in humans (Zangen et al., 2014).

#### **SF-1 dosage as a key regulator of adrenocortical growth and of tumorigenesis**

The critical role of SF-1 as a developmental regulator became evident by the analysis of the phenotype of Sf-1 KO mice (see above). The role for Sf-1 gene dosage in the development of adrenals is demonstrated by the finding that Sf-1 heterozygous mice have hypoplastic adrenals, with a decreased corticosterone and increased ACTH plasma levels, especially after stress (Bland et al., 2000). Also in the adult mouse Sf-1 dosage is critical for compensatory adrenal growth following unilateral adrenalectomy (Beuschlein et al., 2002).

The function of SF-1 in the regulation of adrenocortical growth has a particular relevance to understand the mechanisms of adrenocortical tumorigenesis. Important input came from pediatric adrenocortical tumors studies. These tumors are particularly frequent in southern Brazil and are associated with the presence of the germline R337H TP53 mutation, NR5A1 copy number gain/gene amplification and SF-1 protein overexpression (Ribeiro et al., 2001; Figueiredo et al., 2005; Pianovski et al., 2006; Letouzé et al., 2012). Subsequent studies involving both a human adrenocortical cell line with inducible SF-1 overexpression and a transgenic mouse model bearing multiple copies of the Sf-1 gene showed that an increased SF-1 dosage activates adrenocortical cell proliferation and induces adrenocortical neoplasia (Karpova et al., 2005; Doghman et al., 2007). Moreover, the transcriptional activation function (AF2 domain) of SF-1 is necessary for its role in adrenocortical cell proliferation. Interestingly, those tumors develop in the subcapsular region of the Sf-1 transgenic adrenal glands and express the gonadal markers Gata4 and AMH, derived most probably from undifferentiated adrenogonadal precursors (Looyenga and Hammer, 2006). Transcriptome analysis revealed that SF-1 regulates new and distinct categories of gene involved in multiple functions according to its dosage (Doghman et al., 2013) (see above). Altogether, it appears that SF-1 dosage plays an important role during adrenal development and tumorigenesis.

#### **Role of SF-1 in embryonic stem (ES) cells differentiation**

The role of SF-1 in stem cells differentiation into steroid-producing cells was first investigated in 1997 by Crawford and colleagues (Crawford et al., 1997). They reported that the forced expression of SF-1 directed mouse ES cells into the steroidogenic cell lineage, although the steroidogenic capacity of these cells was very limited. Upon SF-1 transfection, human mesenchymal stem cells (MSC) were shown to be successfully converted into steroidogenic cell lineage appearing to be glucocorticoid- rather than testosterone-producing cells (Yawaza et al., 2006). Moreover, Gondo et al., reported that steroid hormone production was observed for more than 112

d when bone marrow-derived MSC were infected with SF-1 by an adenoviral vector (Gondo et al., 2008). Interestingly introduction of LRH1 (Liver-specific receptor, NR5A2), another member of the NR5A family, resulted in differentiation of human MSCs into steroidogenic cells (Yawaza et al., 2009). In 2011, Yazawa et al., reported a method for differentiating mouse ES cells into steroid-producing cells through tetracycline-controlled transcriptional activation of SF-1 (Yazawa et al., 2011).

It has been demonstrated that human ES/iPS (induced Pluripotent Stem) cells can be differentiated into steroid-producing cells by first inducing them to differentiate into the mesodermal lineage and then introducing SF-1 (Sonoyama et al., 2012). The steroidogenic cells obtained expressed mRNAs encoding adrenocortical or gonad-specific steroidogenic enzymes and produced a wide variety of steroid (Sonoyama et al., 2012). All these findings indicate that SF-1 could work as a differentiating factor for the steroidogenic differentiation of multipotent stem cells and open new perspectives for future regenerative therapy.

## Mutations

Studies carried out on human patients provided genetic evidence for the pivotal role of SF-1 in endocrine development. Several SF-1 mutations have been described in humans and are associated with a wide variety of human reproductive phenotypes, like 46,XY disorders of sex development (DSD), hypospadias, anorchia, male infertility or primary ovarian insufficiency in women and adrenal failure (reviewed in Lin and Achermann, 2008; Ferraz-de-Souza et al., 2011; Human Gene Mutation Database). Several of these genetic alterations are represented by heterozygous nonsense or frameshift mutations which alter RNA stability through nonsense-mediated decay or produce a truncated non-functional protein (reviewed in Lin and Achermann, 2008). Other genetic alterations are present as nucleotide polymorphisms or deletions.

Several novel heterozygous missense mutations identified provide interesting insights into SF-1 structure-function correlation. As described below, most of those missense mutations lie within the primary or accessory DBD affecting highly-conserved aminoacid residues (reviewed in Lin and Achermann, 2008). These genetic alterations interfered with DNA binding and inhibited transcriptional activation in transient gene expression assays.

The earliest studies on NR5A1 mutations were based on single case reports (Achermann et al., 1999; Achermann et al., 2002). They focused on the rare group of 46,XY females exhibiting primary adrenal

failure, severe gonadal dysgenesis and persistence of Müllerian structures (a phenotype resembling Sf-1 null knockout mice). The first patient showed a heterozygous de novo G35E mutation which disrupts the P-box primary DNA-binding motif within the first zinc finger of SF-1 DBD (see Protein description), thus resulting in diminished target gene binding and transactivation (Achermann et al., 1999; Ito et al., 2000a; Tremblay et al., 2003). The second patient exhibited a homozygous R92Q mutation within the A-box (see Protein description), resulting in a variable and partial loss of SF-1 activity (Achermann et al., 2002).

Other reported mutations were shown to impair transcriptional activity through abnormal DNA binding (V15M, M78I, G19S), perturbed sub-nuclear localization (V15M, M78I, as well as another mutation in the DBD, C33S, Köhler et al., 2008) or by disrupting the putative ligand-binding pocket (L437Q) (Lin et al., 2007). Another mutation affecting the proximal part of the SF-1 LBD is R255L, a de novo heterozygous change identified in a girl showing primary adrenal insufficiency at 14 months of age (Biaison-Lauber and Schoenle, 2000). The mutant SF-1 protein was shown to be transcriptionally inactive, but without a dominant negative effect.

Further, in-frame deletions and frameshift and missense mutations have been detected in four families with histories of both 46,XY DSD and 46,XX primary ovarian insufficiency and in 2 of 25 patients with sporadic ovarian insufficiency (Lourenço et al., 2009). Functional studies showed that those mutations substantially impaired SF-1 transactivation activity. One of the mutation identified by Lourenço et al. in the LBD is D293N. The mutated protein partly activated both CYP11A1 and CYP19A1 promoters (Lourenço et al., 2009). Homozygosity for D293N caused either 46, XY complete gonadal dysgenesis or 46, XY DSD, suggesting a pivotal role of this domain in modulating male sex differentiation.

NR5A1 mutations can affect also the hinge region of the protein (see Protein structure). The first mutation discovered in the hinge region was G146A (WuQiang et al., 2003). The mutated protein shows slightly diminished transactivation activity on the CYP11A promoter and the CYP19 promoter II. However, the mutation does not alter protein expression or stability and does not display dominant negative effect.

Recent studies in patients with novel NR5A1 mutations have shown no clear genotype-structure-function-phenotype correlation (Camats et al., 2012). Thus, further investigation is necessary to better understand the broad range of clinical manifestations produced by SF-1 mutations.

## Implicated in

### **SF-1 expression in prostate cancer**

Recently, it has been reported that SF1 is expressed in prostate cancer cells but not in normal prostate. SF-1 expression stimulates local and autonomous steroid production necessary to induce proliferation and survival that contribute to aggressive prostate cancer (Lewis et al., 2014).

### **SF-1 overexpression and adrenal tumorigenesis**

Important insights into the key role of SF-1 dosage came from pediatric adrenocortical tumors analysis. Using comparative genomic hybridization (CGH) and SNP array profiling, a high frequency of chromosomal aberrations and amplification of 9q33-q34 region, harboring the SF-1 gene, emerged as the most consistent finding in a majority childhood adrenocortical tumors (Figueiredo et al., 1999; Figueiredo et al., 2005; Pianovski et al., 2006; Letouzé et al., 2012). SF-1 overexpression has been shown to increase proliferation of human adrenocortical cells, and to induce adrenocortical tumors in Sf-1 transgenic mice (Doghman et al., 2007) (see above). Further studies have shown that the levels of SF-1 expression represent a stage-independent prognostic indicator in patients with adrenocortical cancer (Sbiera et al., 2010). SF-1 dosage is then considered as a critical factor in adrenocortical tumorigenesis (reviewed in Lalli, 2010).

### **SF-1 expression in endometriosis**

SF-1 is expressed in endometriotic cells whereas it is not usually detected in normal endometrium and can exert a role in the pathogenesis of endometriosis (Xue et al., 2007; reviewed in Bulun et al., 2009). SF-1 expression leads to an aberrant activation of StAR and CYP19 genes expression and to an increase of the endogenous synthesis of estrogen within endometriotic tissue, a key causative factor in the disease. This aberrant expression seems to be explained by modifications in the regulation of SF-1 expression by DNA methylation of CpG islands in the promoter, intron 1, and exon 2/intron 3 regions (Xue et al., 2014).

### **46 XY, development of sex disorders (DSD)**

#### **Note**

Heterozygous NR5A1 mutations emerge as a relatively frequent finding in patient with 46,XY DSD from typical to severe phenotype, but without adrenal insufficiency. The patients present a phenotype of ambiguous or female external genitalia at birth and small inguinal testes. Müllerian structures may be present or absent, and Wolffian structures are often seen. There is a significant biochemical evidence of partial gonadal dysgenesis with impaired androgen synthesis, that contributes to

the phenotype, as shown by low levels of testosterone, inhibin  $\beta$  and AMH and an elevation of FSH (reviewed in Lin and Achermann, 2008).

NR5A1 mutations have also been detected in 46, XY patients with severe hypospadias and small inguinal testes due to partial dysgenesis and /or a reduced androgen synthesis (Lin et al., 2007). SF-1 was also considered as a candidate gene for bilateral anorchidia based on the study of a cohort of 24 boys where one boy carried a heterozygous NR5A1 mutation. He presented one absent testis, one very small testis with undetectable AMH in early infancy, and later a testis atrophy in childhood (Philibert et al., 2007). However the patient's twin brother who harbored the same mutation underwent normal puberty suggesting that, despite incomplete penetrance of NR5A1 mutations, SF-1 could participate in maintaining the testis.

A study identified heterozygous NR5A1 mutations, localized in the hinge region and proximal LBD of the protein, associated with spermatogenic failure (from moderate oligospermia to azoospermia) in healthy men, widening the range of gonadal phenotypes associated with NR5A1 mutations (Bashamboo et al., 2010).

### **Adrenal insufficiency**

Given the central role of SF-1 in adrenal development and steroidogenesis, several studies have looked for NR5A1 mutations in children and adults with primary adrenal insufficiency. Only few cases have been described of NR5A1 mutations that also produce adrenal insufficiency in addition to gonadal defects (Achermann et al., 1999; Achermann et al., 2002; Malikova et al., 2014). A single case of a prepubertal girl where adrenal insufficiency was associated with apparent normal ovarian development has been reported (Biaison-Lauber and Schoenle, 2000).

In another study, no NR5A1 mutations were identified in a small cohort of girls diagnosed with adrenal hypoplasia (Lin et al., 2006).

Similarly, no significant NR5A1 changes were found in boys affected by adrenal hypoplasia without DAX1 mutations (Lin et al., 2006). Thus, NR5A1 mutations seem not to be a common cause of primary adrenal failure in boys without reproductive dysfunction or 46,XY DSD.

### **Primary ovarian insufficiency (POI)**

#### **Note**

NR5A1 mutations have been identified in familial and sporadic forms of 46,XX primary ovarian insufficiency (Lourenço et al., 2009). These 46XX patients presented either primary or secondary amenorrhea at variable ages. Primary gonadal failure was associated with elevated LH and FSH and low estrogen levels. These NR5A1 mutations, detected in

subjects with anomalies of ovarian development and function, are associated with an impairment of transactivation on the CYP11A1 and CYP19A1 promoters. Detection of NR5A1 mutations in 46, XX women with ovarian failure shows that SF-1 is an important factor in ovarian development and function in humans.

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