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Topic 1.11

Human disorders caused by nuclear receptor gene mutations*

John C. Achermann[1] and J. Larry Jameson[2,‡]

[1]Centre for Human Growth and Maturation, Institute of Child Health and Department of Medicine, University College London, London, UK; [2]Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University Medical School, Chicago, IL 60611, USA

Abstract: The identification of naturally occurring nuclear receptor mutations highlights the critical role that many of these transcription factors play in human endocrine development and function. Inactivating mutations in the ligand-dependent nuclear receptors (TRβ, VDR, ERα, GR, MR, AR) are well characterized in patients with conditions such as androgen insensitivity syndrome (AIS) and vitamin D resistance. On the other hand, mutations in TRβ act in a dominant negative manner to cause hormone resistance. Inactivating mutations in orphan nuclear receptors have also been identified (PPARγ2, HNF4α, PNR, NURR1, SF1, DAX1, SHP) and reveal important developmental and metabolic functions for this group of receptors with previously elusive physiologic roles. In addition to loss of function mutations, receptor activation can result from mutations that confer constitutive activity or altered ligand responsiveness to the receptor (MR, AR), or from genetic duplication (DAX1) or the expression of fusion proteins (RARA, PPARγ1). Together, these naturally occurring mutations provide fascinating insight into key structural and functional receptor domains to reveal the diverse role nuclear receptors play in human biology.

INTRODUCTION

Nuclear receptors are a family of transcription factors that play a crucial role in the development and function of many endocrine and non-endocrine tissues [1–3] (see also <http://bc.georgetown.edu/nrr/nrr.html>). The best-characterized of these are the ligand-dependent nuclear receptors (TRβ, VDR, ERα, GR, MR, AR). These receptors are activated by specific high-affinity hormone ligands such as thyroid hormone and estrogen. Inactivating mutations in the genes that encode these factors have been described in patients with a range of endocrine disorders (Table 1) [4].

In contrast, the majority of nuclear receptors identified to date are termed "orphan" nuclear receptors [5]. Although some "adopted" orphan receptors have been shown to respond to various low-affinity metabolic ligands, such as fatty acid derivatives and bile acids (PPARγ2, HNF4α) [6], most orphan nuclear receptors have no known natural ligands and may function in a ligand-independent manner. Orphan nuclear receptors are expressed in a wide range of endocrine and nonendocrine tissues, and inactivating mutations in several orphan nuclear receptors have now been identified in patients (Table 2).

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‡Corresponding author: Address: Department of Medicine, The Feinberg School of Medicine, Northwestern Memorial Hospital Galter Pavilion, Suite 3-150, 251 East Huron Street, Chicago, IL 60611-2908, USA; Tel.: (312) 926-9436; Fax: (312) 926-7260; E-mail: ljameson@northwestern.edu

Table 1 Loss of function mutations in ligand-dependent nuclear receptors.

Receptor	Disorder	Features	Locus	Inherit.	Mutation	Number*
Thyroid β	Resistance to thyroid hormone	Small goiter Hyperactivity Tachycardia	3p24.3	AR, AD, S	P, D	>100
Vitamin D	Hereditary Vitamin D-resistant rickets	Hypocalcemia Rickets Short Statute Alopecia	12q12-14	AR	P	>20
Estrogen α	Estrogen resistance	Tall stature Delayed epiphyseal fusion Osteoporosis (m)	6p25.1	AR, S	P	1
Glucocorticoid	Glucocorticoid resistance	Hypertension Hyperandrogenism Infertility Fatigue	5q31	AR, AD, S	P	8
Mineralocorticoid	Pseudohypo-aldosteronism Type 1	Hypotension Salt loss (mild, remits with age)	4q31.1	AD	P	13
Androgen	Androgen insensitivity syndrome	Undermasculinization (complete, partial) Male infertility	Xcen-q13	XL, S	P, D	>300

AR = autosomal recessive, AD = autosomal dominant, S = somatic cell mutation, XL = X-linked, P = point mutation, D = deletion; *approximate numbers of different mutations in each receptor are shown.

Table 2 Loss of function mutations in "orphan" nuclear receptors.

Receptor	Features	Locus	Inherit.	Mutation	Number
PPARγ2	Obesity Insulin resistance	3p25	AD	P	4
HNF4α	MODY 1	20q12-13.1	AD	P	10
PNR	Enhanced S cone syndrome	15q23	AD, AR	P	12
NURR1	Schizophrenia/BPD	2q22-23	AD	P	4
SF-1	Primary adrenal failure XY sex-reversal Müllerian structures	9q33	AD, AR	P	3
DAX1	Adrenal hypoplasia congenita Hypogonadotropic hypogonadism Impaired spermatogenesis	Xp21.3-21.2	XL	P, D	>80
SHP	Mild obesity	1p36.1	AD	P	9

BPD = bipolar disorder

Inactivating mutations in nuclear receptors impair receptor function and gene transcription through mechanisms that include reduced ligand binding, abnormal cofactor interactions, loss of hetero- or homo-dimerization, abnormal nuclear localization or impaired DNA binding to target genes. In contrast, increased receptor activity can arise from alternative mechanisms such as nuclear receptor activation or altered ligand selectivity (e.g., MR, AR). Dominant negative mutations of a specific receptor isoform (e.g., TRβ), duplication of a gene that functions in a dosage-dependent manner (e.g., over-

expression of *DAX1*), or the expression of gene fusion products (PPARγ1, RARA) can also lead to specific disease phenotypes (Table 3).

Table 3 Alternative mechanisms causing nuclear receptor disease.

Mechanism	Receptor	Features
Activating mutation	Mineralocorticoid	Hypertension, exacerbated by pregnancy
	Androgen	Prostate carcinoma
	PPARγ2	Obesity
Loss of function of a specific receptor isoform	Thyroid receptor β	Hyperactivity/ADHD Tachycardia
Overexpression due to gene duplication	DAX1	Dosage-sensitive sex reversal
Fusion proteins	FAS/ERα	Human cancer cell lines
	PAX8/PPARγ1	(prostate, breast, cervix, bladder)
	EWS/TEC (NOR1)	Thyroid follicular carcinoma
	PML/RARA	Extraskeletal myxoid chondrosarcomas Acute promyelocytic leukemia
CAG trinucleotide repeat	Androgen	↑ CAG: X-linked spinal and bulbar muscular atrophy ↓ CAG: Prostate cancer susceptibility

In this review, we provide an overview of hereditary diseases associated with nuclear receptor mutations in humans, and highlight several examples where naturally occurring mutations provide insight into receptor action. The effect of receptor polymorphisms on human health will be discussed only briefly, as the significance of many of these associations is still unclear.

MUTATIONS IN LIGAND-DEPENDENT NUCLEAR RECEPTORS

Thyroid receptor β (TRβ) (NR1A2): Resistance to thyroid hormone

The syndrome of resistance to thyroid hormone (RTH) is characterized by reduced target tissue responsiveness to circulating thyroid hormones, and results in elevated levels of serum T4 and T3 and an inappropriately nonsuppressed TSH [7,8]. Some of these patients are relatively asymptomatic, reflecting the fact that the elevation in circulating thyroid hormone levels is sufficient to partially compensate for the generalized resistance (GRTH). Other patients experience symptoms reminiscent of thyrotoxicosis, including weight loss, tremor, palpitations, insomnia, failure to thrive, growth abnormalities, and attention-deficit hyperactivity disorder [4]. These symptoms may reflect a predominant pituitary resistance (PRTH) due to TRβ mutations, allowing activation of normal TRα receptor isoforms in the heart and other tissues by high circulating thyroid hormone levels [9]. In practice, however, considerable overlap in clinical features is seen among individuals, whether they harbor the same or different mutations.

The vast majority of RTH cases have an autosomal dominant pattern of inheritance and heterozygous mutations within the ligand-binding domain (LBD) of the TRβ receptor [7,8]. Missense mutations in this region tend to cluster within three specific domains, and interfere with ligand binding and/or coactivator interaction to exert a "dominant negative" effect on wild-type receptor activity. Consequently, TRβ activation of target genes in the presence of ligand is impaired, but basal repression in the absence of ligand is unaffected. In some cases, TRβ mutations may enhance corepressor binding [10]. Further evidence of a dominant negative effect is evidenced by a severe phenotype (developmental delay and growth retardation) in a boy homozygous for a mutation in TRβ in comparison to individuals with a complete deletion of one or both TRβ alleles [11,12]. Somatic mutations and alternative

splicing of TRβ has been described as the basis of resistance to feedback in a subset of TSH-secreting pituitary tumors.

Vitamin D receptor (VDR) (NR1I): Hereditary vitamin D-resistant rickets

The vitamin D receptor binds the active form of vitamin D (1,25-dihydroxyvitamin D) with high affinity to mediate its effects on calcium homeostasis, skeletal development and bone mineralization. Mutations in the VDR cause hereditary vitamin D-resistant rickets (HVDRR) [13]. Clinical features include bone pain, muscle weakness, hypotonia, convulsions, and clinical and radiological evidence of rickets within the first few months of life. Many children have sparse hair, while some have total alopecia. Laboratory investigations reveal hypocalcemia, elevated 1,25-dihydroxyvitamin D, and elevated PTH due to secondary hyperparathyroidism. More than 20 different homozygous mutations have been reported throughout the DNA- and ligand-binding domains of the VDR. Point mutations within the DNA-binding domain (DBD) tend to have a more severe effect and are usually associated with alopecia. Variations in the severity of LBD mutations may reflect differences in ligand-binding affinity and/or dimerization with RXR [14]. Rarely, partial deletions of the VDR locus or intronic mutations that cause exon skipping have been reported. As most patients with HVDRR do not respond to supraphysiological doses of vitamin D, adjunctive treatment with high dose intravenous calcium (to circumvent the impaired intestinal calcium absorption) has been used to treat this form of rickets. The relation between VDR polymorphisms and bone mineral density remains under investigation [15].

Estrogen receptor α (ERα) (NR3A1): Estrogen resistance

Only one human ER mutation has been described to date, in a male who presented at age 28 with tall stature (204 cm) and continued linear growth, and delayed epiphyseal fusion despite otherwise normal pubertal development [16]. He had increased serum estradiol, FSH and LH, and decreased sperm viability; impaired glucose tolerance and hyperinsulinemia with clinical evidence of acanthosis nigricans; abnormal serum lipids and evidence of early coronary atherosclerosis; a bone mineral density 3.1 SD below the mean; and resistance to estrogen treatment. Mutational analysis revealed a homozygous R157X mutation in ERα that caused premature truncation of the receptor, including the DNA- and ligand-binding domains. Other family members who are heterozygous for this mutation are phenotypically normal. Although this is the only report of an ERα mutation to date, these findings provide clear evidence for the profound influence of this receptor on many aspects of human reproduction, growth, bone mineralization, metabolism, and cardiovascular health. The effects of ERα mutations in women, or mutations in the ERβ isoform, are unknown. The influence of somatic point mutations, splice variants of ER isoforms and ER cofactors in tumors, such as breast cancer, is under active investigation [17,18], as are the effects of ER polymorphisms and variants on bone mineral density, and in cardiovascular and psychiatric disease [19].

Glucocorticoid receptor (GRα) (NR3C1): Familial glucocorticoid resistance

Mutations in GRα cause familial glucocorticoid resistance (FGR) [20]. This syndrome has a range of clinical features and can be inherited as an autosomal dominant or autosomal recessive condition, depending on the underlying molecular mechanism or severity of the mutation. Patients with FGR often feel fatigue, but other signs of glucocorticoid insufficiency are rare because the ACTH-driven elevation in cortisol compensates for receptor insensitivity. A consequence of this ACTH drive is the elevation of mineralocorticoids and androgens, resulting in (1) hypertension, hypokalemia, and metabolic alkalosis; and (2) hirsutism, acne, male-pattern baldness, oligomenorrhea, and infertility, respectively.

Most GRα mutations are located within the LBD of the receptor and affect ligand binding and transactivation. Patients or carriers with heterozygous mutations often have a milder clinical phenotype,

although dominant negative LBD mutations appear to inhibit nuclear translocation of the wild-type receptor (I557N, I747N) or impair receptor/coactivator (p160) interactions (I749M) [21,22]. The clinical and biochemical effects of homozygous mutants in GRα tend to be more severe. For example, a homozygous V729I mutation has been reported in a boy with pseudoprecocious puberty, and a homozygous V571A mutation has been found in a girl with clitoral enlargement and labial fusion at birth (Note: this patient was also heterozygous for a CYP21/21-hydroxylase conversion) [23]. Polymorphisms in GRα have been reported in association with central obesity and somatic GRα mutations have been reported in a patient with glucocorticoid-resistant leukemia.

Mineralocorticoid receptor (MR) (NR3C2): Autosomal dominant or sporadic pseudohypoaldosteronism type I

To date, 13 heterozygous mutations have been described in the MR of patients with the autosomal dominant or sporadic forms of pseudohypoaldosteronism type 1 (PHA1) [24]. This condition is characterized by neonatal salt wasting (dehydration, hypotension, hyperkalemia), elevated aldosterone and plasma renin activity, and resistance to mineralocorticoid replacement therapy. Clinical and biochemical features tend to remit with age, in contrast to the autosomal recessive form of PHA1, due to mutations in the amiloride-sensitive epithelial sodium channel (EnaC). Most missense mutations in the MR reported to date are located within the LBD and abolish aldosterone-dependent transactivation in an in vitro assay system [25].

A fascinating report describes a heterozygous S810L mutation within the ligand-binding pocket of the MR in members of a kindred who developed early-onset hypertension (before age 20), and the affected females had an extreme elevation of blood pressure during pregnancy [26]. This missense mutation causes constitutive MR activity and altered receptor specificity, so that progesterone and other steroids lacking 21-hydroxyl groups become MR agonists (Fig. 1). This report illustrates how naturally occurring mutations or variations in receptor structure can alter ligand responsiveness, and has potential implications for the effect of environmental modulators on receptor function within a population.

Androgen receptor (AR) (NR3C4): Androgen insensitivity syndrome (AIS)

More than 200 different inactivating mutations in the AR have been reported in patients with various forms of the X-linked androgen insensitivity syndrome (see Topic 1.10, ref. 27; also <http://www.mcgill.ca/andogendb/>). These mutations can occur throughout the gene, although missense mutants usually affect critical amino acids in the DNA- or ligand-binding domains of the protein. Truncation mutants usually cause a severe phenotype of complete AIS (CAIS) in which genotypic males (46XY) show a total lack of virilization and have a female phenotype. These patients often present in adolescence with a failure of menstruation (no uterus is present) or inguinal masses (testes). Missense mutations in the AR are associated with both complete and partial forms of AIS (PAIS). Patients with PAIS have genital ambiguity or penoscrotal hypospadias at birth. The karyotype is 46XY, no Müllerian structures are detected, and biochemical tests (increased testosterone, increased LH) reflect androgen resistance. Finally, missense mutations with a milder loss of function have been identified in men with oligospermic infertility. These changes may have subtler effects, such as disruption of receptor/coactivator (e.g., TIF2) interactions [28].

An unusual feature of the AR is the variable polyglutamine and polyglycine tandem repeats in the amino-terminal region of the receptor. Expansion of the polyglutamine tract (from 20-23 to 43-65) triggers X-linked spinal and bulbar muscular atrophy (Kennedy disease) [29]. This condition is sometimes associated with decreased virilization, reduced sperm production, testicular atrophy, and infertility. Less severe repeat expansions (>28) have been associated with an increased risk of impaired spermatogenesis, and with moderate undermasculinization of males (46XY) compared to controls [30].

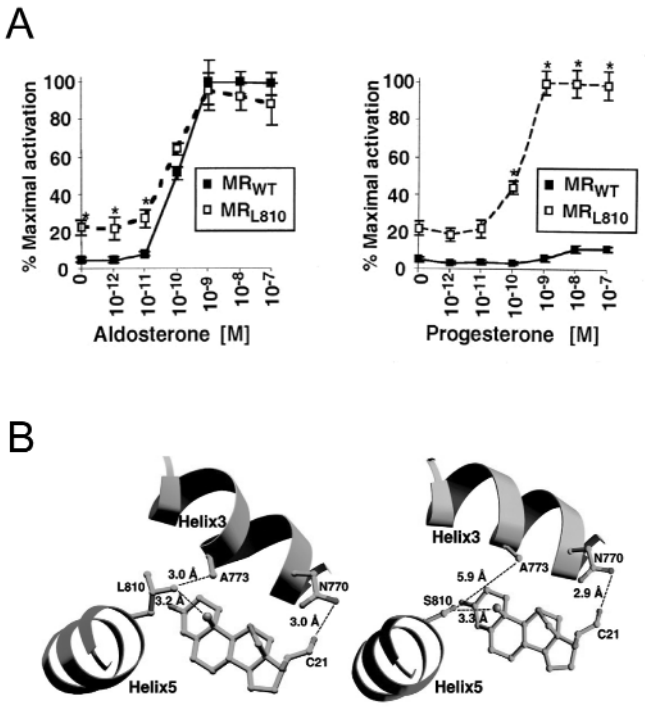

Fig. 1 An "activating" mutation in the mineralocortioid receptor has been described in a kindred with early-onset hypertension exacerbated during pregnancy. (A) The S810L mutant receptor has constitutive activity and inappropriate responsiveness to progesterone. (B) The wild-type serine (5.9 Å, right) to leucine (3.0 Å, left) change at position 810 results in a gain of van der Waals interaction between helix 5 and helix 3 that substitutes for interaction of the 21-hydroxyl group with helix 3 in the wild-type receptor (reproduced with permission from [26]).

Several studies have examined the role of the AR in prostate cancer. Shorter polyglutamine repeats can be associated with more aggressive forms of tumor, and several somatic AR mutations have been discovered in metastatic prostate tumors and human prostate cancer cell lines. The best-characterized of these is the T877A mutation, which alters the structure of the ligand-binding pocket and confers inappropriate responsiveness to progesterone, glucocorticoids, and other C17, C19, and C21 circulating steroids at concentrations found in vivo [31–33]. These studies have important implications for the treatment of prostate cancer, and once again highlight how receptor mutations can alter specificity to potential environmental modulators.

ORPHAN NUCLEAR RECEPTORS

Although the orphan nuclear receptors have no known natural ligands or respond with only low affinity to certain metabolic compounds, they are emerging as important targets for manipulation by environmental modulators and drugs. Mutations in several orphan nuclear receptors have now been identified.

Perioxisome proliferator-activated receptor-γ (PPARγ2) (NR1C3)

PPARγ2 is the target for the thiazolidinedione (TZD) group of drugs used in the treatment of type 2 diabetes. PPARγ2 is expressed in many tissues, including the liver, muscle and fat, and regulates adipocyte differentiation and atherogenesis as well as insulin sensitivity and lipid metabolism. PPARγ2

can be activated by eicosapentaenoic acid, 9-hydroxyoctadecadienoic acid and 15-deoxyprostaglandin J_2.

Given its role in the adipocyte, PPARγ2 was considered a candidate gene for human obesity, and the P115Q mutation was found in 4 out of 121 German patients with a body mass index greater than 29 [34]. This mutation disrupts phosphorylation of an adjacent serine residue, and results in a gain-of-function mutation that mediates enhanced adipocyte differentiation in vitro. In contrast, germline loss-of-function missense mutations (P467L, V290M) in PPARγ2 have been identified in patients from two kindred with severe insulin resistance, hirsutism, diabetes mellitus, and hypertension, but normal body mass index [35]. These heterozygous mutations destabilize helix 12 and impair transcriptional regulation in a dominant negative manner. Furthermore, a heterozygous R425C mutation in PPARγ2 has been identified in a woman who had early-onset diabetes mellitus, hypertriglyceridemia, and hirsutism, and developed lipodystrophy of the extremities and face at age 50 [36].

PPARγ may also have a role in tumor biology, as somatic inactivating mutations in PPARγ2 have been found in four out of 55 sporadic colon tumors [37]; a H449H polymorphism may be associated with a predisposition to glioblastoma; TZDs may modulate the growth of certain breast and prostate cancer cells; and a translocation resulting in a PAX8/PPARγ1 fusion protein has been detected in a subset of thyroid follicular carcinomas. The role of the P12A polymorphism in PPARγ2 in tumorigenesis, obesity, or metabolic dysfunction remains under investigation [for review, see ref. 38].

Hepatocyte nuclear factor-4 α (HNF4α) (NR2A1)

The orphan nuclear receptor HNF4α is expressed in the liver, pancreas, intestine, and kidney, where it is involved in the network of transcription factors that regulate hepatic gene expression and glucose, cholesterol, and fatty acid metabolism. Mutations in HNF4α have been found in patients with maturity-onset diabetes of the young, type 1 (MODY1), a relatively rare form of early-onset diabetes [39]. Most of these mutations are heterozygous changes that impair transcription through their effects on DNA binding, homodimerization, or nuclear localization, but do not appear to function in a dominant negative manner [40,41].

HNF4α can regulate transcription of target genes directly, but may exert many of its actions through the regulation of HNF1α (which is mutated in patients with MODY3). Indeed, the identification of a disrupted HNF4α binding site in the HNF1α promoter in an Italian family with MODY provides further evidence for the importance this pathway in hepatic gene regulation and glucose homeostasis [42]. This cascade of transcription factors likely involves intricate feedback mechanisms, as HNF1α, HNF1β, and IPF1 binding sites have been identified in the HNF4α promoter (P2), and a change in the IPF1 element cosegregates with diabetes in a large MODY kindred [43]. Furthermore, it is possible that HNF4α activity is modulated by metabolic intermediates, such as long-chain fatty acyl-CoA thioesters, which could represent an additional level of control in this complex regulatory network.

Photoreceptor-specific nuclear receptor (PNR) (NR2E3)

PNR is expressed in the outer nuclear layer of the neurosensory retina and plays a key role in human photoreceptor development. Several PNR mutations have been described in patients with enhanced S cone syndrome, a condition involving increased sensitivity to blue light, visual loss, night blindness and progressive retinal degeneration [44,45]. These patients have an increase in the number of S (short wavelength, blue) cones at the expense of other photoreceptor subtypes (L/M; red/green), suggesting that PNR has an important function in determining photoreceptor fate and maintaining retinal integrity [45]. Retinitis pigmentosa has been described in a cohort of Portuguese patients with PNR mutations [46], and features of retinal dysplasia and degeneration have also been identified in the rd7/rd7 mouse, which harbors a large deletion in the coding region of Nr2e3.

Nuclear receptor-related-1, NURR1 (NR4A2)

Homozygous NURR1 knockout mice fail to develop midbrain dopaminergic neurons and heterozygous animals have reduced dopamine levels. NURR1 was therefore considered a candidate gene in patients with neuropsychiatric disorders. Three partially inactivating missense mutations in NURR1 have been reported in a cohort of 324 patients with schizophrenia or manic-depression. An insertion in an untranslated exon was found in two of 177 schizophrenic patients, but not in the controls [47,48]. The true significance of NURR1 mutations in these patients, or in patients with Parkinson's disease, remains to be seen.

Steroidogenic factor-1 (SF1) (NR5A1)

SF1 regulates the transcription of an array of target genes involved in gonadal and adrenal development, steroidogenesis, and reproduction, by binding as a monomer to variations on an extended ER half-site (PyCA AGGTCA). Consistent with this pivotal role in gene transcription, homozygous deletion of SF1 in mice results in gonadal and adrenal agenesis, complete 46XY sex-reversal with persistent Müllerian structures in males, impaired gonadotropin release, abnormalities of the ventromedial hypothalamus and spleen, and obesity. Heterozygous animals have a milder adrenal phenotype.

SF1 mutations have been described in two patients (46XY) with complete sex-reversal, testicular dysgenesis, Müllerian structures, and primary adrenal failure. The first patient has a de novo heterozygous mutation (G35E) in the P-box of the first zinc finger of SF1 [49]. As this motif interacts with the major groove sequence (AGGTCA) to determine DNA-binding specificity, the P-box change affects SF1 binding and transactivation of many target genes [50]. Recently, a homozygous R92Q mutation in the A-box of SF1 has been reported in a patient with a similar phenotype [51]. Heterozygous carriers are normal. The A-box region stabilizes receptor monomer binding by forming a secondary interface with the minor groove of the DNA (PyCA). Thus, a *heterozygous* P-box mutation causes a severe clinical phenotype, whereas a *homozygous* A-box change is necessary for such a phenotype to occur (Fig. 2). Together, these cases confirm that SF1 plays a major role in the development and function of endocrine systems in humans, and reveal the importance of functional gene dosage effects when one factor regulates many different target genes.

The role of SF1 in ovarian function is less clear. The reported presence of ovaries in a girl with primary adrenal failure because of a heterozygous mutation in SF1 suggests that SF1 is not necessary

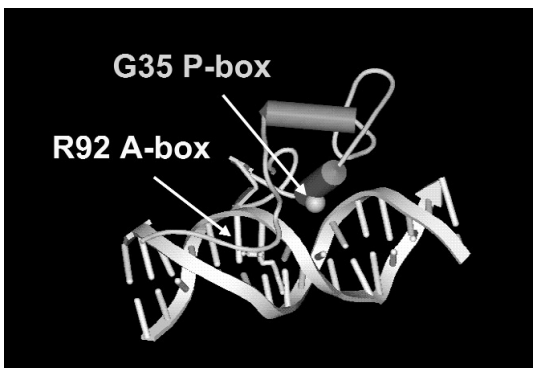

Fig. 2 Model of SF1 binding based on the crystal structure of nerve growth factor-induced-B (NGFI-B) bound to DNA as a monomer. The positions of amino acid 35, within the P-box and the amino acid 92, within the A-box, are indicated by arrows. The P-box amino acids bind to the half-site sequence (variations on AGGTCA) within the major groove of DNA, whereas the A-box is believed to bind to the 5′-flanking sequence (T/CCA) within the minor groove of DNA (reproduced with permission from [51]).

for ovarian differentiation [52]. Whether this SF1 mutation will impair estrogen biosynthesis at the time of puberty or folliculogenesis remains to be seen.

DAX-1 (NR0B1)

DAX1 is an atypical orphan nuclear receptor because of its conserved LBD, and it has an amino-terminal repeat motif structure instead of the classical DNA-binding domain. Functional studies show that DAX1 is a repressor of gene transcription and of SF1 mediated transcriptional regulation. Inactivating mutations or deletions in DAX1 cause X-linked adrenal hypoplasia congenita. More than 80 different mutations have been reported in more that 100 patients or families with this condition. Affected boys usually experience primary adrenal failure in early infancy or throughout childhood and hypogonadotropic hypogonadism (HH) emerges at puberty for boys treated with steroid replacement. DAX1 is expressed in the pituitary gonadotropes as well as the hypothalamus, and HH probably represents a combined defect at both these levels. Furthermore, studies of the *Ahch* (*Dax1*) knock-out mouse have revealed a crucial role for Dax1 in testis development and spermatogenesis. Limited data from patients with X-linked AHC suggest that DAX1 is involved in spermatogenesis in humans, too.

Most patients with X-linked AHC have nonsense or frameshift mutations that truncate the carboxyterminus of DAX1 and severely impair its function as a transcriptional repressor. Missense mutations in DAX1 are less common and cluster within the putative ligand binding domain [55]. Variant phenotypes associated with DAX1 mutations include extreme delayed puberty in female carriers of DAX1 mutations in one family [56], and HH in the absence of adrenal dysfunction in a woman homozygous for a truncation mutation in DAX1 through gene conversion [57]. An adult-onset form of X-linked AHC has also been described in two patients who experienced partial HH and mild adrenal failure [58,59]. The missense mutations found in these patients (Y380D, I439S) exhibit partial loss of function in transient gene expression assays, consistent with the mild clinical phenotype.

Small heterodimeric partner (SHP) (NR0B2)

SHP is an atypical orphan nuclear receptor that closely resembles DAX1 in its carboxy-terminal region, but lacks a conserved DNA-binding motif. SHP is expressed in the liver, intestine and pancreas, and is believed to play a role in lipid metabolism and bile acid synthesis through its interactions with related orphan nuclear receptors, such as FTF (NR5A2) and HNF4α (NR2A1). Given these associations, SHP was considered a candidate gene for patients with MODY. Five different missense mutations were found in six patients from a cohort of 173 Japanese patients with early-onset diabetes [60]. However, as all six individuals were obese, a cohort of 101 nondiabetic subjects with early-onset obesity were screened and SHP mutations were found in an additional six individuals. Thus, mutations in SHP were proposed as a cause of excess weight in a subset of Japanese subjects with mild obesity.

CONCLUDING REMARKS

Naturally occurring mutations in nuclear receptors cause a broad spectrum of endocrine, metabolic, psychiatric, and even ophthalmological conditions. These features highlight the important role this family of transcription factors play in human biology. Studying patients and families with nuclear receptor mutations provides insight into many key functional domains and mechanisms of action for these proteins, including variations in ligand responsiveness, cofactor interaction, nuclear trafficking, and DNA targeting. The combination of clinical investigation and an understanding of basic biology should help unravel whether mutations in other nuclear receptors are responsible for human disease phenotypes, as well as the possible implications of activating and inactivating mutations in the receptors described in this review. Finally, the recent reports of altered ligand-binding specificity due to mutations in the ligand-binding domains of the MR (S810L) and a somatic AR mutation found in prostate cancer (T877A)

show that nuclear receptors are key targets for modulation not only by endogenous ligands, but may also be potential targets for modulation by a host of drugs and environmental agents.

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