Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-.

Familial or Sporadic Adrenal Hypoplasia Syndromes

Eleni Magdalini Kyritsi, MD, PhD
Endocrinologist, Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, "Aghia Sophia" Children's Hospital, Athens, Greece.
madeleine.2007@hotmail.com

Amalia Sertedaki, PhD
Research Associate, Molecular Endocrinology Laboratory, Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, "Aghia Sophia" Children's Hospital, Athens
aserted@med.uoa.gr

Evangelia Charmandari, MD, MSc, PhD, MRCP(UK), CCST(UK)
Professor of Pediatrics, Pediatric Endocrinology, Division of Endocrinology and Metabolism, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, "Aghia Sophia" Children's Hospital, Athens
evangelia.charmandari@googlemail.com

George P Chrousos, MD, PhD, MACP, MACE, FRCP(UK)
Professor of Pediatrics and Endocrinology, Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, "Aghia Sophia" Children's Hospital, Athens, Greece. Division of Endocrinology and Metabolism, Biomedical Research Foundation of the Academy of Athens, Athen
chrousge@med.uoa.gr
Corresponding author.

Created: October 22, 2018.

ABSTRACT

Congenital adrenal hypoplasia is a rare cause of primary adrenocortical failure, which was first described in 1948. During the last two decades, the genetic basis for several forms of familial adrenal insufficiency syndromes has been elucidated. The molecular mechanisms for these disorders involve a broad spectrum of cellular and physiologic processes, including metabolism, nuclear protein import, oxidative stress defense-mechanisms, and regulation of cell cycle. Adrenal hypoplasia can occur: 1) secondary to defects in transcription factors involved in pituitary development or 2) defects in ACTH synthesis and secretion; 3) as a primary defect in the development of the adrenal gland; 4) as part of rare syndromes associated with adrenal hypoplasia/aplasia, which are inherited in an autosomal recessive or autosomal dominant manner; and 5) in the context of chromosomal abnormalities. Early diagnosis and management are crucial because of the life-threatening nature of the condition. Depending on the etiology, adrenal crisis may occur in early infancy or could insidiously develop over the course of childhood or adolescence. Moreover, some of these conditions previously thought to occur only in childhood, may also be diagnosed later in adulthood and present with variable phenotypes, including isolated infertility or disorders of sex differentiation. The clinical manifestations of primary adrenal insufficiency (PAI) result from deficiency of all adrenocortical hormones (aldosterone, cortisol, androgens). The acute presentation can be precipitated by physiologic stress, such as surgery, trauma, or an intercurrent infection. Patients may present with signs and symptoms of complete adrenal insufficiency, usually early in life, including hypoglycemic convulsions, hyponatremia, hyperkalemia, metabolic acidosis or later with hyperpigmentation, vomiting and poor weight gain. It should be remembered, that the most common cause of PAI in children is congenital adrenal hyperplasia due to 21-hydroxylase deficiency and can be excluded by measuring baseline or ACTH-stimulated 17-hydroxyprogesterone levels in serum. Screening for autoimmune Addison disease includes detection of 21-hydroxylase antibodies. Males with negative 21-hydroxylase antibodies should be tested for adrenoleukodystrophy measuring very–long-chain fatty acids concentrations in plasma. The presence of alacrima in patients with PAI should raise suspicion for Triple A syndrome, whereas the combination of PAI and hypogonadotropic hypogonadism in a male patient point towards X-linked adrenal *hypoplasia congenita*. To date, molecular genetic testing is commercially available for the identification of several genes involved in adrenal hypoplasia syndromes. The early identification of these diseases can have important prognostic and therapeutic implications for patients with respect to surveillance for associated conditions, initiation of early treatment or screening of family members who are at risk. Adrenal insufficiency is potentially life threatening, thus treatment should be initiated as soon as the diagnosis is confirmed, or sooner if the patient presents in adrenal crisis. Therapy consists of life-long replacement therapy with glucocorticoids and mineralocorticoids. Hypogonadism or other associated disorders should be treated appropriately. Screening of family members for the disease or carrier status may also be indicated and can be critical for family planning. When a monogenic cause of adrenal failure is identified, genetic counseling is indicated. For complete coverage of all related areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

INTRODUCTION

The adrenal glands consist of two anatomically and functionally distinct subunits, the cortex and the medulla. The adrenal cortex secretes glucocorticoids, mineralocorticoids and androgens. The glucocorticoid, cortisol, is secreted by the cells of the intermediate *zona fasciculata*. Its secretion is tightly regulated by the hypothalamic corticotropin-releasing hormone (CRH) and vasopressin (AVP) and by the pituitary adrenocorticotropic hormone (ACTH) (1). Glucocorticoids regulate a broad spectrum of physiologic functions essential for life and play an important role in the maintenance of basal and stress-related homeostasis. The mineralocorticoid, aldosterone, is produced by the outer adrenal *zona glomerulosa*. This steroid regulates water and electrolyte homeostasis and its secretion is primarily under the control of the renin-angiotensin system, although it may be weakly influenced by ACTH. The adrenal androgens, dehydroepiandrosterone (DHEA), its sulfate (DHEA-S) and androstenedione, are secreted by the inner *zona reticularis* under the control of ACTH.

CONGENITAL ADRENAL HYPOPLASIA

Congenital adrenal hypoplasia is a rare cause of primary adrenocortical failure, which was first described in 1948. It has an estimated frequency of 1:12,500 live births (2). During the last decade there have been significant advances in our understanding of the genetic etiology of several forms of adrenal insufficiency with a presentation in infancy or childhood. Several of these conditions affect adrenal development and are commonly known as adrenal hypoplasia. Adrenal hypoplasia may be due to (3-9):

1. Secondary to defects in transcription factors involved in pituitary development (e.g. HESX1, LHX4, SOX3) or defects in ACTH synthesis (TPIT), processing and release (e.g. POMC or PC1);
2. Part of an ACTH resistance syndrome [MC2R/ACTH receptor, MRAP, AAAS (triple A syndrome), StAR, CYP11A1, MCM4, NNT, TXNRD2, GPX1, PRDX3 mutations];
3. A primary defect in the development of the adrenal gland itself (primary/congenital adrenal hypoplasia; X-linked form/DAX1 gene mutations or deletions, autosomal recessive form/SF-1 gene mutations or deletions, autosomal recessive form of uncertain etiology, IMAGe syndrome, MIRAGE syndrome, Familial steroid-resistant nephrotic syndrome with adrenal insufficiency due to SGPL1 deficiency);
4. Part of rare syndromes associated with adrenal hypoplasia/aplasia, which are inherited in an autosomal recessive (Meckel-Gruber syndrome, Pena-Shokeir syndrome, Pseudotrisomy 13, Hydrolethalus syndrome, Galloway-Mowat syndrome) or autosomal dominant (Pallister-Hall syndrome) manner; and
5. In the context of chromosomal abnormalities (tetraploidy, triploidy, trisomy 18, trisomy 21, 5p duplication, monosomy 7 and the 11q syndrome), which are often associated with central nervous system (CNS) abnormalities.

There are two distinct histological patterns of the adrenal cortices in this rare syndrome, the miniature adult and cytomegalic forms. In the miniature adult form of adrenal hypoplasia congenital (AHC), the small amount of residual adrenal cortex is composed primarily of permanent adult cortex with normal structural organization. The miniature adult form is either sporadic or inherited in an autosomal recessive manner, and is frequently associated with abnormal CNS development, including anencephaly or pituitary gland abnormalities.

In the cytomegalic form of AHC, the residual adrenal cortex is structurally disorganized with scattered irregular nodular formations of eosinophilic cells, with the adult permanent zone absent or nearly absent. Enlarged cells are present, some with abundant vacuolated cytoplasm. The cytomegalic form is generally considered to be X-linked, but there may be one or more autosomal genes associated with this phenotype (6, 10, 11).

Genetic causes of adrenal hypoplasia and aplasia syndromes are summarized in Table 1. However, this review focuses on ACTH resistance syndromes and disorders of adrenal gland development.

TABLE 1:

Genetic Causes of Adrenal Hypoplasia and Aplasia

	Genetics	**Associated Clinical Manifestations**
Adrenal dysgenesis **Primary/congenital adrenal hypoplasia**		
Pallister-Hall syndrome	GLI3 -autosomal dominant, 25% de novo mutation -transcription factor, mediator of Shh signaling	Hypothalamic hamartomas, mesoaxial and postaxial polydactyly, bifid epiglottis, imperforate anus, genitourinary anomalies, laryngotracheal cleft, pituitary insufficiency

	Genetics	Associated Clinical Manifestations
Adrenal dysgenesis **Primary/congenital adrenal hypoplasia**		
Meckel-Gruber syndrome	MKS1 -autosomal recessive -protein localized to the basal body, required for formation of the primary cilium in ciliated epithelial cells	Cystic renal disease, CNS malformation – occipital encephalocele, polydactyly, hepatic abnormalities
Pena-Shokeir syndrome	-DOK7 (homozygous truncating mutation) non-catalytic cytoplasmic adaptor protein that is expressed specifically in muscle and is essential for the formation of neuromuscular synapses -RAPSN (homozygosity for a frameshift mutation) postsynaptic protein that connects and stabilizes acetylcholine receptors at the neuromuscular junction -autosomal recessive	Arthrogryposis, facial anomalies, IUGR, camptodactyly, fetal akinesia, polyhydramnion, pulmonary hypoplasia, cardiac defects, intestinal malrotation
Pseudotrisomy 13	Genetic cause unclear; thought to be autosomal recessive	Holoprosencephaly, polydactyly, craniofacial anomalies
Hydrolethalus syndrome	HYLS1 -protein incorporated into centrioles as they are formed, required for the formation of cilia -autosomal recessive	Hydrocephaly, micrognathia, polydactyly, abnormal genitalia, congenital heart defects, respiratory organ defects
Galloway-Mowat syndrome	WDR73 • protein found in the cytoplasm during interphase, but accumulates at the spindle poles and astral microtubules during mitosis • reduced expression results in abnormalities in the size and morphology of the nucleus -autosomal recessive	Nephrotic syndrome, microcephaly, encephalopathy, diaphragmatic hernia
X-linked	NR0B1 (DAX1)	Males: hypogonadotropic hypogonadism. In some cases, normal puberty, central or gonadotropin-independent precocious puberty Infertility, attention deficit disorder, short stature, growth hormone deficiency, inappropriate tall stature, renal ectopy, macrophalia in infancy Females carrying homozygous or heterozygous mutations: isolated hypogonadotropic hypogonadism or extreme pubertal delay, respectively
Xp21 contiguous gene syndrome	Deletion of genes for Duchenne muscular dystrophy, glycerol kinase, and NR0B1	Duchenne muscular dystrophy, glycerol kinase deficiency, psychomotor retardation, hepatic iron deposition
SF-1 linked	NR5A1 (SF-1) -autosomal recessive or dominant	XY sex reversal, gonadal insufficiency, 46,XX ovotesticular/testicular DSD, gonadoblastoma, germ cell neoplasia in situ (GCNIS), splenic

	Genetics	**Associated Clinical Manifestations**
Adrenal dysgenesis **Primary/congenital adrenal hypoplasia**		
		anomalies, ovarian insufficiency Microdeletions of chromosome 9q33.3, involving NR5A1: genitopatellar syndrome, developmental delay, ovotestes, XY sex reversal
IMAGe syndrome	CDKN1C -imprinted mode of inheritance/maternal transmission	Intrauterine growth retardation, metaphyseal dysplasia, genital abnormalities, hypercalcemia, dysmorphic facial features, soft tissue calcifications, growth hormone deficiency, skeletal abnormalities, hydronephrosis, hypercalciuria-associated nephrocalcinosis, oligohydramnios
MIRAGE syndrome	SAMD9 -autosomal dominant	Myelodysplasia, infection, restriction of growth, genital phenotypes, enteropathy, dysmorphic features, bronchopulmonary dysplasia, neurologic abnormalities, skeletal abnormalities, renal defects, apneas, reduced body fat
Metabolic Disorders		
Familial steroid-resistant nephrotic syndrome with adrenal insufficiency	SGPL1 -autosomal recessive	Adrenal calcifications, ichthyosis, immunodeficiencies, dermatologic, ophthalmologic, neurologic, skeletal and genital abnormalities, hypothyroidism, muscular hypotonia, fetal demise, fetal hydrops, facial dysmorphism, hypocalcemia, dilated cardiomyopathy, intestinal malrotation, capillary leak syndrome.
ACTH Resistance Syndromes		
Familial glucocorticoid deficiency (FGD) Type 1	MC2R gene mutations -autosomal recessive	Hyperpigmentation, tall stature, characteristic facial features, such as hypertelorism and frontal bossing, lethargy and muscle weakness but normal blood pressure (mostly normal production of MC)
FGD Type 2	MRAP gene mutations --autosomal recessive	Hyperpigmentation, normal height, hypoglycemia, lethargy, and muscle weakness, but normal blood pressure (mostly normal production of MC), obesity
Nonclassic CLAH (FGD variant)	partial loss-of-function mutations of StAR* CYP11A1 - autosomal recessive	Milder phenotype of FGD with no gonadal derangement potentially hypogonadism and compromised fertility in adulthood
Variant of FGD (DNA repair defect)	MCM4 gene mutations -autosomal recessive	Growth failure, microcephaly, increased chromosomal breakage, natural killer cell deficiency, recurrent viral infections
Variant of FDG (Deficiency of mitochondrial radicals detoxification)	NNT -autosomal recessive TXNRD2 -autosomal recessive GPX1 PRDX3 -autosomal recessive	Precocious puberty associated with testicular nodules**, hypothyroidism, hypertrophic cardiomyopathy, azoospermia associated with testicular adrenal rests and elevated FSH levels, plagiocephaly Left ventricular noncompaction¶ Only glucocorticoid deficiency Dilated cardiomyopathy‡ Only glucocorticoid deficiency Only glucocorticoid deficiency
Triple A syndrome (Allgrove's syndrome)	AAAS gene mutations -autosomal recessive	Achalasia, alacrima, deafness, mental retardation, hyperkeratosis, neurodegeneration, short stature, osteoporosis, xerostomia, nasal speech, angular cheilitis, glossitis and fissured tongue, enamel defect, poor wound healing, hypolipoproteinemia type IIb, scoliosis, pes

	Genetics	Associated Clinical Manifestations
Adrenal dysgenesis Primary/congenital adrenal hypoplasia		
		cavus, long QT syndrome, microcephaly, dysmorphic features, premature loss of permanent teeth

AAAS=achalasia, adrenocortical insufficiency, alacrima syndrome. CDKN1C= Cyclin-dependent kinase inhibitor 1C (p57, Kip2). CLAH=Congenital Lipoid Adrenal Hyperplasia. CYP11A1= Cytochrome P450, family 11, subfamily A, polypeptide 1. DAX1= Dosage sensitive sex reversal, Adrenal hypoplasia congenita, critical region on X chromosome, gene-1. DOX7=Docking protein 7. FGD: familial glucocorticoid deficiency. FSH: Follicle stimulating hormone. GLI3=gene responsible for Greig cephalopolysyndactyly syndrome (GCPS), Pallister-Hall syndrome (PHS), Preaxial polydactyly type IV and Postaxial polydactyly type-A1 and B. GPX1= Glutathione Peroxidase 1. HYLS1= Hydrolethalus syndrome protein 1. IMAGe=Intrauterine growth restriction (IUGR), Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genitourinary abnormalities. MC=Mineralocorticoids. MC2R=Melanocortin 2 receptor. MCM4= Minichromosome maintenance complex component 4. MIRAGE=Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes and Enteropathy. MKS1=gene responsible for Meckel syndrome, type 1 and Bardet-Biedl syndrome type 13. MRAP=Melanocortin 2 receptor accessory protein. NNT= Nicotinamide nucleotide transhydrogenase. NR0B1= Nuclear Receptor subfamily 0, group B, member 1. NR5A1= Nuclear receptor subfamily 5 group A member 1. PRDX3=Peroxiredoxin 3. RAPSN=Receptor-associated protein of the synapse. SAMD9=Sterile Alpha Motif Domain-Containing 9. SF-1=Steroidogenic factor 1. SGPL1= Sphingosine-1-Phosphate Lyase 1. Shh= Sonic hedgehog. StAR= Steroidogenic acute regulatory protein. TXNRD2= Thioredoxin reductase 2. WDR73= WD repeat domain 73.

* To date, nine StAR mutations have been reported in patients with NCLAH (30).

** Leydig cell adenoma identified in one case (40).

¶ Heterozygous loss of function mutations in NNT gene (42).

‡ TXNRD2 mutations have been detected in 3 out of 227 patients with a diagnosis of dilated cardiomyopathy, however, no data are available on their adrenal function (15).

ADRENAL HYPOPLASIA AS PART OF AN ACTH RESISTANCE SYNDROME

ACTH resistance syndromes include two distinct genetic disorders, both of which are inherited in an autosomal recessive manner and are characterized by ACTH insensitivity:

1. Familial Glucocorticoid Deficiency (FGD)
2. Allgrove syndrome or Triple A syndrome

Familial Glucocorticoid Deficiency (FGD)

Familial (isolated) glucocorticoid deficiency (FGD), which is also known as hereditary unresponsiveness to ACTH, is a rare autosomal recessive disorder characterized by glucocorticoid deficiency (12, 13). The underlying genetic defect is known in approximately 70% of patients with FGD.

CLINICAL AND LABORATORY FEATURES OF FGD

Patients with FGD are usually diagnosed during the neonatal period or in early childhood. However, the oldest affected member of the kindred, carrying MCM4 and TXNRD2 mutations (see Genetics below), presented at the age of 8.5 years and 10.8 years, respectively (14, 15). Patients with FDG may present with hypoglycemic seizures, hyperpigmentation, recurrent infections, transient neonatal hepatitis, failure to thrive, collapse and coma. The long-term neurological sequelae of FGD can vary from learning difficulties to spastic quadriplegia, which may reflect the severity and number of hypoglycemic episodes in childhood. There may be a family history of unexplained neonatal death, history of other family member(s) affected with FGD and/or parental consanguinity (12, 16).

The clinical manifestations of FGD reflect resistance to ACTH. The typical hormonal profile in FGD is a combination of low cortisol but high plasma ACTH concentrations, in the presence of normal plasma renin activity and aldosterone concentrations. Most patients with FGD have markedly elevated ACTH concentrations, which correlate with the degree of ACTH resistance. Hyperpigmentation is often observed during the first months of life owing to the effect of ACTH on the melanocortin-1 receptors in melanocytes (12).

ADRENAL IMAGING

In the MRI or CT scans, the adrenal glands appear small in size.

HISTOPATHOLOGY

Absence of fasciculata or reticularis cells and disorganization of glomerulosa cells have been observed (17).

GENETICS

FGD was first described by Shepard et al. (18) in 1959, when he reported two siblings with "familial Addison's disease". It took 30 years for the first inactivating ACTH receptor mutations to be detected (19, 20). To date, FGD has been associated with mutations in seven genes: MC2R (ACTH receptor/melanocortin 2 receptor) (OMIM 202200), MRAP (MC2R accessory protein) (OMIM 607398), StAR (steroidogenic acute regulatory protein) (OMIM 201710), CYP11A1 (cytochrome P450, family 11, subfamily A, polypeptide 1) (OMIM 613743), NNT (nicotinamide nucleotide transhydrogenase) (OMIM 614736), MCM4 (the mini chromosome maintenance-deficient 4 homolog gene) (OMIM 609981), TXNRD2 (thioredoxin reductase 2) (OMIM 617825), GPX1 (Glutathione Peroxidase 1) and PRDX3 (peroxiredoxin 3) (9, 21,). Mutations in the MC2R and MC2R accessory protein (MRAP) account for approximately 50% of all cases.

The ACTH receptor MC2R is a 7-membrane G-protein coupled receptor located almost exclusively in the adrenocortical cells. To date, more than 50 mutations have been described in the MC2R gene (Human Gene Mutations Database, www.hgmd.cf.ac.uk) and represent the most common cause of FGD (25% of cases, FGD type 1) (8, 16). Some of them are shown in Table 2. FGD type 1 patients usually present in early childhood. Tall stature has been observed in some cases (22).

TABLE 2:

Mutations of the MC2R in FGD Patients

Mutation	Probable Effect of Mutation	Reference
p.D107G	Failure to bind ACTH	Aza-Carmona et al,[13].
p.R145C	Trafficking defect	Aza-Carmona et al,[13].
c.459_460insC	Translation frame shift after codon 154 and a premature termination codon at 248 of the MC2R mRNA (p.I154fsX248)	Al Kandari et al,[43].
p.Leu225Arg	Unknown	Akin et al,[44].
K289fs	Impaired cell surface expression (Loss of C terminus of MC2R)	Hirsch et al,[45].
G116V	Impaired cell surface expression	Collares et al,[46].
T159K	Impaired cell surface expression	Elias et al,[47].
D20N	Possible loss of ligand affinity	Chung et al,[48].
H170L	Loss of signal transduction	Chung et al,[48]
D103N	Loss of signal transduction and loss of ligand affinity	Berberoglu et al,[49], Chung et al,[48].
R137W	Loss of signal transduction	Ishii et al,[50].
P273H	Possible structural disruption	Wu et al,[51].
S120R	Possible structural disruption	Tsigos et al,[20,52].
R201X	Truncated receptor	Tsigos et al,[20].
S74I	Possible loss of ligand affinity	Clark et al,[19].
I44M	Possible loss of ligand affinity	Weber et al,[53].
Y254C	Possible structural disruption	Tsigos et al,[52,54].
R146H	Loss of signal transduction	Weber et al,[53].
R128C	Loss of signal transduction	Weber et al,[53] .
L192fs	Truncated receptor	Weber et al,[53].
D107N	Loss of ligand affinity and loss of signal transduction	Naville et al,[55], Chung et al,[48].
C251F	Possible structural disruption	Naville et al,[55].
G217fs	Truncated receptor	Naville et al,[55].
p.Pro281GlnfsX9	Frameshift mutation	Delmas et al,[56].

In 2005, a second gene was identified, located at 21q22.1 and encoding MC2R accessory protein (MRAP), a 19-kDa single-transmembrane domain protein. In humans, MRAP is expressed in the adrenal cortex, pituitary, brain, testis, ovary, breast, thyroid, lymph node, skin, and fat. This protein serves as an essential cofactor of MC2R to promote its trafficking from the endoplasmic reticulum to the cell surface and subsequent signaling in response to ACTH (16, 23-25). Mutations in MRAP are responsible for a further 15-20% of FGD cases (FGD type 2). Most patients with FGD type 2 present in the neonatal period or in very early infancy. However, missense MRAP mutations are associated with a milder phenotype and late onset adrenal insufficiency (AI) (26). Interestingly, obesity has been reported in a patient harboring homozygous MRAP mutations and his heterozygous family members, whereas the only unaffected member of the family had normal weight (25). Studies on Mrap-/- mice demonstrated the important role of MRAP plays in both steroidogenesis and the regulation of adrenal cortex zonation. Mrap-/- mice were shown to have isolated GC deficiency with normal aldosterone and catecholamine production and small adrenal glands with gross impairment of the adrenal capsular morphology and cortex zonation. Furthermore, progenitor cell differentiation was significantly impaired, with dysregulation of WNT4/b-catenin and sonic hedgehog pathways (27). MRAP mutations are summarized in Table 3.

TABLE 3:

Mutations of the MRAP in FGD Patients

Mutation	Probable Effect of Mutation	References
c.106+2_3dupTA	Skipping of exon 3 (No protein or lack transmembrane domain)	Jain et al,[16].
c.3G>A	Unknown	Chung et al,[57], Collares et al,[46], McEachern et al,[58].
c.175T>G	Full-length protein with amino acid change-impaired cAMP generation	Hughes et al,[59].
c.76T>C	Full-length protein with amino acid change-impaired cAMP generation	Hughes et al,[59].
c.106+2insT	Skipping of exon 3 (No protein or lack transmembrane domain)	Chung et al,[57], Metherell et al,[23].
c.106+1G>T	Skipping of exon 3 (No protein or lack transmembrane domain)	Chung et al,[57], Metherell et al,[23]
c.106+1G>A	Skipping of exon 3 (No protein or lack transmembrane domain)	Chung et al,[57], Metherell et al,[23].
c.106+1G>C	Skipping of exon 3 (No protein or lack transmembrane domain)	Chung et al,[57], Metherell et al,[23].
c.106+1delG	Skipping of exon 3 (No protein or lack transmembrane domain)	Chung et al,[57]., Metherell et al,[23]., Akin et al[60].
c.33C>A	Shortened protein if translated	Chan et al,[12].
c.17-23delACGCCTC	Shortened protein if translated	Modan-Moses et al,[61].
c.128delG (p.V44X)	Frameshift mutation causing a premature termination (V44X) in exon 4	Metherell et al,[23], Rumie et al,[25]

Interestingly, mutations in steroidogenic acute regulatory protein (StAR) and more rarely cytochrome P450 family 11 subfamily A member 1 (CYP11A1) have also been detected in patients with FGD (StAR: approximately 5% of FGD patients). Mutations in these two enzymes usually result in Congenital Lipoid Adrenal Hyperplasia (CLAH), a severe disorder with both adrenal and gonadal steroid insufficiencies. However, certain, partial loss-of-function mutations may be associated with a milder phenotype with no gonadal derangement, termed non-classic CLAH (NCLAH). To date, nine StAR mutations have been reported in patients with NCLAH. Of note, affected individuals require life-long monitoring of both adrenal and gonadal function because their disorder may evolve. Hypogonadism and infertility may occur in adulthood. (28-31).

Recently, mutations in the mini chromosome maintenance-deficient 4 (MCM4) homolog gene have been identified in an Irish travelling community presenting with a variant of FGD. These patients had short stature, chromosomal breakage, natural killer cell deficiency and progressive primary adrenal insufficiency (PAI) characterized by ACTH resistance with glucocorticoid deficiency and normal mineralocorticoids (MC) levels. Typically, patients started with normal adrenal function and developed PAI over time. The MCM4 gene, mapped on 8q11.2 chromosome, is part of a heterohexameric helicase complex, which is important for DNA replication and genome integrity. MCM4 deficiency leads to genomic instability and is associated with increased incidence of cancer and developmental defects. Therefore, it is recommended that patients carrying this mutation are followed-up closely. The c.71-1insG splice site mutation found in the Irish travelling community was predicted to lead to a frameshift with a prematurely terminated translation product (p.Pro24ArgfsX4) (32, 33).

NNT (nicotinamide nucleotide transhydrogenase), a highly conserved gene, encodes a redox-driven proton pump of the inner mitochondrial membrane. This enzyme uses energy from the mitochondrial proton gradient to produce high concentrations of NADPH. Detoxification of reactive oxygen species (ROS) in mitochondria by glutathione peroxidases (GPX) depends on this NADPH for regeneration of reduced glutathione (GSH) from oxidized glutathione (GSSG) to maintain a high GSH/GSSG ratio (Figure 1). The adrenal cortex contains high amounts of P450 steroid enzymes, which use NADPH for their catalytic activity. Its function is therefore very sensitive to ROS (34). ROS may suppress StAR protein synthesis and thus inhibit steroidogenesis (9). In addition, the peroxiredoxin system (PRDX), another antioxidant defense mechanism which removes H_2O_2 and lipid peroxides also requires NADPH (9, 34). PRDX3 is a mitochondrial protein highly expressed in human adrenals. Inactivation of PRDX3 results in accumulation of H_2O_2, activation of p38 MAPK signaling pathways, suppression of StAR protein synthesis and inhibition of steroidogenesis (9, 35). Mutations in GPX1 and PRDX3 have been rarely identified in patients with FGD (9, 36).

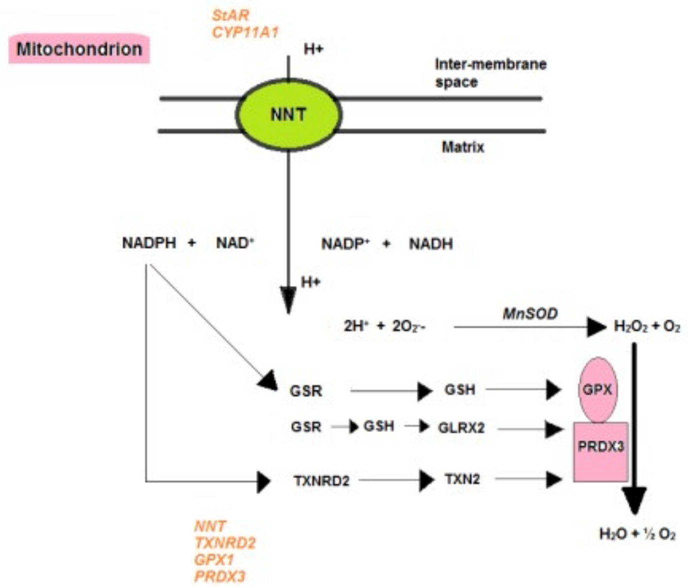

Figure 1.

Detoxification of reactive oxygen species in the mitochondria. NNT (nicotinamide nucleotide transhydrogenase) is a key enzyme, located in the inner mitochondrial membrane, that plays an important role in maintaining the mitochondrial redox balance. It utilizes the electrochemical proton gradient to generate NADPH from NADH and NADP. NNT provides high concentrations of NADPH for detoxification of H2O2 by the glutathione and thioredoxin pathways. Manganese superoxide dismutase catalyzes the conversion of the superoxide radical O2.- to H2O2. The peroxiredoxin system (PRDX), another antioxidant defense mechanism, which removes H2O2 and lipid peroxides also requires NADPH. NNT loss would result in compromised NADPH production, thereby rendering the mitochondria more susceptible to oxidative stress. Modified by Prasad et al (34) and Flück (9). StAR: Steroidogenic acute regulatory protein; CYP11A1= Cytochrome P450, family 11, subfamily A, polypeptide 1; GSR: glutathione reductase; GSH: reduced glutathione; TXNRD2: thioredoxin reductase 2; TXN2: thioredoxin 2; GLRX2: glutaredoxin 2; NNT: nicotinamide nucleotide transhydrogenase; PRDX3: peroxiredoxin 3; GPX: glutathione peroxidase; MnSOD: manganese superoxide dismutase.

NNT mutations account for 5–10% of FGD patients. The first mutations in the NNT gene were identified six years ago in 20 patients with FGD (candidate region localized on chromosome 5p13–q12), in whom mutations of MC2R, MRAP and StAR had not been detected. A novel homozygous missense mutation at exon 5 of the NNT gene was subsequently reported in a Japanese patient and was predicted to have a loss-of-function effect (c.644T>C, p.Phe215Ser) (37, 38). In mice with Nnt loss, higher levels of adrenocortical cell apoptosis and impaired glucocorticoid production were observed. NNT knockdown in a human adrenocortical cell line resulted in impaired redox potential and increased ROS levels.

It is of great interest, that two patients from non-consanguineous parents of East Asian and South African origin were diagnosed with FGD at the ages of 21 and 8 months respectively, caused by compound heterozygous mutations in NNT, i.e. a heterozygous intron 20 mutation (pseudoexon activation) in combination with a heterozygous stop-gain mutation in exon 3 of NNT gene (p.Arg71) (21).

Recent studies provide new insights into the effects of NNT deletion. Altered mitochondrial morphology, lower ATP content and increased ROS levels have been observed in fibroblasts derived from a patient harboring biallelic NNT mutations (35). Most recently, it was shown that both NNT loss and overexpression can negatively affect steroidogenesis and cause redox imbalance, resulting in reduced protein levels of two mitochondrial antioxidant enzymes (Prdx3 and thioredoxin reductase 2/Txnrd2) and CYP11A1. Transcriptomic analysis of Nnt−/− mice demonstrated upregulation of heat shock proteins, alpha- and beta-hemoglobins, possibly reflecting activations of compensatory mechanisms to cope with oxidative stress (39).

To date, more than 40 pathogenic variants of NNT gene have been identified. They are scattered throughout the gene, including abolishment of the initiating methionine, and splice, missense and nonsense mutations (35, 40, www.hgmd.cf.ac.uk). Phenotypic heterogeneity has been observed among patients carrying the same mutation or within the same family. Unlike “classic FGD”, adrenal dysfunction is not restricted to glucocorticoid deficiency, but may include mineralocorticoid deficiency as well (35, 40). AI is usually diagnosed around the first year of life, may be severe and present with hypoglycemic seizures

Although, NNT mutations have been known to affect preferentially the adrenal glands, all tissues rich in mitochondria may be affected. Extra-adrenal features have been first demonstrated in Nnt-mutant mice, which had reduced insulin secretion and high-fat diet-induced diabetes mellitus, in addition to adrenal dysfunction (27). More recently, extra-adrenal manifestations were also noted in patients harboring homozygous or compound heterozygous NNT mutations, including: precocious puberty associated with testicular nodules (Leydig cell adenoma identified in one case), hypothyroidism, hypertrophic cardiomyopathy, azoospermia associated with testicular adrenal rests and elevated FSH levels and mild plagiocephaly (40, 41).

Of note, heterozygous loss of function mutations in NNT have been recently identified in two patients presenting with left cardiac ventricular noncompaction, an autosomal-dominant cardiomyopathy, which is frequently associated with mitochondrial disorders and cardiac hypertrophy (42).

In 2014, Prasad et al described the first homozygous mutation in the thioredoxin reductase 2 (TXNRD2) gene in an extended consanguineous Kashmiri kindred presenting with FGD (stop gain mutation, c.1341T>G; p.Y447X within exon 15). The selenoprotein TXNRD2, one of three thioredoxin reductases, is mitochondria specific and contributes to the maintenance of redox homeostasis. Particularly high TXNRD2 mRNA levels have been noted in the adrenal cortex compared with the other human tissues investigated, suggesting a susceptibility of the adrenal cortex and especially zona fasciculata to oxidative stress. Given that the final step of cortisol production, which is catalyzed by CYP11B1 in the mitochondria, accounts for approximately 40% of the total electron flow from NAPDH directed at reactive oxygen species production during steroidogenesis, individuals with TXNRD2 and NNT mutations primarily develop glucocorticoid deficiency. Extra-adrenal manifestations, associated with TXNRD2 mutations have also been reported. Txnrd2 deletion in mice is embryonically lethal, resulting in fatal cardiac and hematopoietic defects. In humans, two novel heterozygous mutations in TXNRD2 were identified in 3 of 227 patients with a diagnosis of dilated cardiomyopathy, however, no data are available on their adrenal function (15, 34).

Oxidative stress has been implicated in other causes of adrenal insufficiency, including triple A syndrome and X-linked adrenoleukodystrophy (ALD). In ALD, mutations in ABCD1 (encoding the peroxisomal ABCD transporter) result in the accumulation of very long-chain fatty acids in the tissues and plasma, the toxic effects of which are thought to result from an increase in steady-state ROS production, depletion of glutathione and dysregulation of the cell redox homeostasis. The adrenal and CNS are most susceptible to the disease process (34).

Triple A Syndrome

Triple A syndrome (OMIM 231550) is an autosomal recessive disorder characterized by ACTH-resistant adrenal insufficiency, achalasia of the esophagus, alacrima (absence of tears) and a variety of progressive central, peripheral and autonomic neurological defects (62). It was first described by Jeremy Allgrove in 1978 (63). It has been estimated that Triple A accounts for approximately 1% of all cases of primary adrenal insufficiency (PAI) with a prevalence of 1 per 1,000,000 individuals (64, 65).

CLINICAL FEATURES OF TRIPLE A SYNDROME

The spectrum of clinical manifestations is unique and encompasses a range of phenotypic abnormalities that vary even within families. Alacrima is the most consistent sign, and is attributed to both autonomic dysregulation and structural abnormalities of the lacrimal glands. Achalasia usually presents within the first two decades of life and may precede the adrenal failure by several years (62, 66). Older children/adults usually complain of dysphagia especially for liquids (67). The pathogenesis of achalasia includes a decrease in non-adrenergic and non-cholinergic neurons, as well as a lack of neuronal nitric oxide synthase in autonomic plexus (68). Adrenal failure does not occur in the immediate postnatal period. It usually presents during the first, or more rarely, the second decade of life, suggesting progressive adrenal destruction or degeneration. However, in some cases it may be the presenting symptom leading to the diagnosis of the condition. AI in Triple A syndrome typically manifests as isolated glucocorticoid deficiency, with less than 15% of patients having evidence of mineralocorticoid deficiency (69, 70).

Neurodegenerative disease may include progressive central, peripheral, autonomic neuropathy (pupillomotor, lacrimotor, erectile dysfunction), sensory and motor defects, hyperreflexia, cerebellar dysfunction, bulbospinal syndrome, distal amyotrophy, amyotrophic lateral sclerosis, spastic paraparesis, syringomyelia, atrophy and myofasciculations of the tongue, epilepsy, pyramidal syndrome, dystonia, dysarthria, ataxia, optic atrophy chorea, deafness, mental retardation, Parkinsonism and dementia (64, 65, 67-69).

Based on data of 133 index cases, alacrima was present in all but one patient (99.2%), achalasia in 93.2%, AI in 90.1% and ND in 79.4%. The most common presenting features were AI and achalasia, followed by neurological dysfunction and alacrima. Eight percent of patients developed clinical features of the syndrome in the 3rd to 5th decade of life, however, none presented with AI (70). The above data support previous recommendations, that in cases of presence of alacrima and at least one more symptom of triple A syndrome, adrenal function testing and molecular analysis should be performed (71).

Moreover, a number of associated features have been described in association with Triple A syndrome, including palmo-plantar and punctate hyperkeratosis, short stature, osteoporosis, xerostomia, nasal speech, angular cheilitis, glossitis and fissured tongue, enamel defect, poor wound healing, hypolipoproteinemia type IIb, scoliosis, pes cavus, long QT syndrome, microcephaly and dysmorphic features, such as long narrow face, long philtrum, down-turned mouth, thin upper lip, and lack of eyelashes. Premature loss of permanent teeth has also been reported (62, 64-70, 72-74).

DIAGNOSIS

The diagnosis should be confirmed by the Schirmer test, basal and dynamic endocrine testing, genetic analysis and detailed gastroenterological and neurological evaluation (75). The diagnosis may be extremely challenging, given that the clinical manifestations may evolve at a variable time. Therefore, patients who undergo surgery for achalasia may be at risk of life-threatening adrenal crisis during anesthesia.

GENETICS

The first step towards in identifying the genetic etiology of triple A syndrome was the chromosomal localization by linkage analysis of the gene responsible for this condition to an 6cM area in chromosome 12 (76). Subsequently, homozygote or compound heterozygote mutations were found in the AAAS gene on 12q13 in families with triple A syndrome (77). This gene encodes a 60-kDa nuclear pore protein, termed ALADIN (alacrima-achalasia-adrenal insufficiency, neurologic disorder) (62). AAAS belongs to WD-repeat regulatory protein family, which exhibits wide functional diversity, in that they are involved in signal transduction, RNA processing, vesicular trafficking, cytoskeleton assembly and cell division control. WD-repeat proteins are characterized by the presence of four or more repeating units containing a conserved core of approximately 40 amino acids that usually end with tryptophan-aspartic acid (WD). AAAS mRNA and the ALADIN protein are ubiquitously expressed with predominance in the adrenal and CNS structures in humans and rats (34, 77). ALADIN is the only nucleoporin to be associated with hereditary adrenal disease and the first to be associated with hereditary neurodegenerative disease.

Screening of patients with triple A syndrome worldwide revealed that the IVS14+1G A splice donor mutation is the most common AAAS mutation. In the Puerto Rican and Middle Eastern/southern European populations, the frequent presence of this mutation is the result of a founder effect. A variety of disease-associated missense, nonsense, splice-site and frameshift mutations have been shown to result in either ALADIN deficiency or mis-localization of the abnormal protein, found predominantly into the cytoplasm, suggesting that correct targeting of ALADIN to the nuclear pore complex is required. Splice-site, indel, intronic region, regulatory element and 5′ UTR mutations have been also detected in affected individuals (70). Over 75 different mutations have been described in the literature (www.hgmd.cf.ac.uk), some of which are shown in Table 4 (62, 64, 77-85). However, there is little phenotype/genotype correlation, even between affected siblings, suggesting that other factors may be involved in disease progression (86). A recent review of the literature, showed that AI was more prevalent and diagnosed at a younger age in patients harboring truncating mutations. On the other hand, neurological dysfunction was more prevalent, with an older age at onset, in patients carrying non-truncating mutations (70). In addition, patients with truncating mutations were more likely to present with symptomatic AI, while those with non-truncating mutations with neurological dysfunction.

Table 4.

Mutations of the AAAS Gene

Mutation	**Probable Effect of Mutation**	**Reference**
125C→A	Deduced peptide sequence Q15K	Handschug et al,[77].
869T→C	Deduced peptide sequence S263P	Handschug et al,[77].
333G→A	Deduced peptide sequence W84X	Handschug et al,[77].
561A→G	Deduced peptide sequence H160R	Handschug et al,[77].
552-553delTT	Deduced peptide sequence F157fs	Handschug et al,[77].
869T→C	Deduced peptide sequence S263P	Handschug et al,[77].
1471delC	Deduced peptide sequence S463fs	Handschug et al,[77].
869T→C	Deduced peptide sequence S263P	Handschug et al,[77].
938C→T	Deduced peptide sequence R286X	Handschug et al,[77].
1106C→T	Deduced peptide sequence R342X	Handschug et al,[77].
IVS14+1G→C	Defective nuclear transportation of Ferritin Heavy Chain protein (FTH1)	Storr et al,[62].
p.Q387X	Defective nuclear transportation of Ferritin Heavy Chain protein (FTH1)	Storr et al,[62].
H71fs	Defective nuclear transportation of Ferritin Heavy Chain protein (FTH1)	Storr et al,[62].
R230X	Defective nuclear transportation of Ferritin Heavy Chain protein (FTH1)	Storr et al,[62].
IVS11+1G→A	May interfere with the formation of WD repeats	Sandrini et al,[78].
43C→A	Defective preservation of stability of ALADIN β-strands	Sandrini et al,[78].
c.130delA	Frameshift after phenylalanine at amino acid position 435	Thummler et al,[79].
c.1292-1294delTTCinsA	Change of phenylalanine at amino acid position 431 into a stop codon	Thummler et al,[79].
R194X	Deduced peptide sequence	Marin et al,[80].
p.Ala167Val	Change of alanine at position 167 into valine	Moschos et al,[81].
p.Ser207fs	Frameshift mutation	Krull et al,[82].
c.577C>T	p.Gln193X in exon 7	Yang et al,[83].
c.1062_1063insAC	p.Ser355fsX416 in exon 11 Frameshift mutation	Yang et al,[83].
c.887C>A	p.Ser296Tyr in exon 9	Dumić et al,[84].
c.123+2T>C	Splice defect	Milenkovic et al,[71].
c.1261_1262insG	Truncated protein (p.V421fs), most probably not functional	Milenkovic et al,[71].
c.56A > G	p.Tyr 19 Cys	Capataz Ledesma et al,[85].
10-bp deletion c.1264_1273del	Frameshift introducing an aberrant stop codon after 126 amino acids p.Q422NfsX126	Kurnaz E et al,[64].
c.1144_1147delTCTG	Frameshift with a premature stop codon (p.Ser382ArgfsX33)	de Freitas MRG et al,[65].
c.755G>C	p. (Trp252Ser) missense	Roucher-Boulez F et al,[69].
c.1331+1G>A	Splice-site mutation	Patt H et al,[70].

Oxidative stress may play a role in the pathogenesis of this complex disorder. Data derived from experimental *in vitro* models of the disease, have shown that dermal fibroblasts of patients with triple A syndrome have higher basal intracellular ROS and are more sensitive to oxidative stress than wild-type fibroblasts. It has been suggested, that the failure of the nuclear accumulation of DNA repair proteins, aprataxin, and DNA ligase I together with the antioxidant protein ferritin heavy chain in skin fibroblasts of patients with triple A syndrome may render these cells more susceptible to oxidative stress. A disruption in redox homeostasis is suggested in the ALADIN-deficient adrenal cells with a depletion of reduced GSH, a major endogenous antioxidant and a cofactor of the antioxidant enzyme glutathione peroxidase. Moreover, AAAS knockdown results in cell cycle arrest and an increase in cell death by apoptosis. Increased chromosomal fragility has also been reported (34, 87). ALADIN protein has been shown to localize around the mitotic spindle and at spindle poles in Drosophila and human cells. It interacts with the microsomal protein progesterone receptor membrane component 2 (PGRMC2), regulator of cell cycle and activity regulator of CYP P450 enzymes, as well as with the inactive form of Aurora A, a serine/threonine kinase involved in various mitotic events. Recent studies suggest that ALADIN protein has functions in cell division. Interestingly, mitotic spindle assembly errors have been observed in cultured fibroblasts of patients with Triple A syndrome (88, 89). Finally, AAAS gene deficiency affects steroidogenesis and results in a reduction in StAR and P450c11β protein expression, and consequently in a significant reduction of cortisol production, an effect that is partially reversed with antioxidant N-acetylcysteine treatment (87). In addition, AAAS knock-down induces downregulation of genes coding for 17α-hydroxylase/17,20-lyase (CYP17A1), 21-hydroxylase (CYP21A2) and their electron donor cytochrome P450 oxidoreductase (POR), resulting in decreased production of glucocorticoid and androgen precursors (90).

Mutations in the AAAS gene have been identified in 90-95% of patients with a clinical diagnosis of Triple A syndrome (69, 70). The remaining cases may result from unidentified large deletions, mutations in uncharted intronic or regulatory regions, or mutations in two novel genes that may produce a “triple-A-like” phenotype without AI. GMPPA (guanosine diphosphate (GDP)-mannose pyrophosphorylase A) mutations were reported to cause an autosomal-recessive disorder characterized by achalasia, alacrima, and neurological deficits. Very recently, a homozygous splice mutation in TRAPPC11 gene, encoding for trafficking protein particle complex subunit 11, has been detected in patients presenting with achalasia, alacrima, myopathy and neurological symptoms (91, 92).

PRIMARY/CONGENITAL ADRENAL HYPOPLASIA

Five forms of AHC have been identified: 1) The X-linked form (OMIM 300200) caused by a mutation or deletion of the DAX1 gene (Dosage-sensitive sex reversal Adrenal hypoplasia congenita critical region of the X chromosome gene-1; NR0B1) on the X chromosome; 2) The autosomal recessive form owing to a mutation or deletion of the gene that encodes for the steroidogenic factor 1 (SF-1)/NR5A1 on chromosome 9q33 (OMIM 184757); 3) An autosomal recessive form of uncertain etiology (OMIM 240200); and 4) The IMAGe syndrome (Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital abnormalities) (OMIM 614732) 5) The MIRAGE syndrome (Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes and Enteropathy) (OMIM 617053).

Most recently, mutations in the gene encoding sphingosine-1-phosphate (S1P) lyase 1 (SGPL1), located on chromosome 10q22.1 have been associated with a syndrome comprising primary adrenal insufficiency and steroid-resistant nephrotic syndrome 9, 10) (OMIM: 617575).

X-linked Adrenal Hypoplasia Congenita (AHC)

The incidence of X-linked AHC is unknown. The latest reports estimate it to be less than 1:70,000 live male births (5, 93). X-linked AHC is characterized by infantile-onset acute adrenal insufficiency at an average age of 3 weeks in approximately 60% of affected individuals. Onset in childhood accounts for 40% of the cases, whilst only a few individuals are diagnosed in adulthood due to infertility.

CLINICAL FEATURES OF X-LINKED AHC

Adrenal insufficiency typically presents acutely with vomiting, feeding difficulties, dehydration and shock owing to salt-wasting. Hypoglycemia, frequently presenting with seizures, may be the first symptom. If untreated, adrenal insufficiency may lead to hyperkalemia, metabolic acidosis, hypoglycemia, hypovolemic shock and death. Cryptorchidism may be present. Affected males typically present with delayed puberty due to hypogonadotropic hypogonadism and are infertile. Carrier females may occasionally have symptoms of adrenal insufficiency or hypogonadotropic hypogonadism (5, 94). Imaging studies may reveal small, ectopic, or normal in size adrenal glands (5).

DIAGNOSIS

Primary adrenal insufficiency, as evidenced by hyponatremia, hyperkalemia, metabolic acidosis, low aldosterone and elevated ACTH concentrations in the presence of normal or low 17-hydroxyprogesterone concentrations, in a male infant strongly suggests X-linked AHC (5). Serum cortisol concentrations in the first weeks of life vary from very low to high (95). An ACTH test would detect cortisol deficiency, whilst a GnRH test would most possibly reveal impaired gonadotropin secretion (94, 96, 97).

Elevated 11-deoxycortisol concentrations have been documented in kindreds with DAX1 mutations, but only when determined very early in life. A mouse model that displays elevated 11-deoxycorticosterone concentrations and evidence of hyperplasia of the zona glomerulosa has recently been described. DAX1 testing may be considered in patients with evidence of 11β-hydroxylase deficiency, especially in those with severe salt-wasting (98).

GENETICS

Males with the above manifestations should undergo genetic analysis for the DAX1 gene. The DAX1 gene also known as NR0B1, (Nuclear Receptor subfamily 0, group B, member 1) is located on chromosome Xp21.2 and is responsible for the X-linked AHC (93, 97, 99). The NR0B1 gene (MIM#300473) encodes an orphan member of the nuclear receptor superfamily that is expressed in the hypothalamus, the anterior pituitary, the adrenal glands and the gonads. Nuclear receptors are thought to play a functional role in the establishment and maintenance of steroidogenic tissues. They are transcription factors that regulate gene networks important for reproduction, development and homeostasis in response to various extracellular and intracellular signals. The DAX1 carboxy-terminal domain (CTD) shares high similarity to the ligand-binding domain (LBD) of other nuclear receptors. The amino-terminal region is an atypical DNA binding domain, consisting of 3.5 repeats of 66–67 amino acid repeat motifs (100). At this time, DAX1 lacks a known ligand and is therefore named an orphan nuclear receptor.

The molecular mechanism of DAX1 action during development remains unclear. However, many studies have shown that DAX1 functions as a transcriptional repressor of steroid biosynthesis pathways regulated by other nuclear receptors, such as the SF1-mediated transactivation of genes StAR, 3β-hydroxysteroid dehydrogenase and cholesterol side-chain cleavage enzyme (P450scc). In addition to SF1, it acts as a repressor to other nuclear receptors, such as the estrogen receptor (ER) (101)**,** progesterone receptor (PR), glucocorticoid receptor (GR) (102), androgen receptor (AR) (103) and the liver receptor homologue-1 (LRH-1) (104). DAX1 has also been proposed to act as a shuttling RNA binding protein associated with ribonucleoprotein structures in the nucleus and polyribosomes in the cytoplasm, raising the possibility that it plays an additional regulatory role in post-transcriptional processes (105). Other studies have demonstrated that DAX-1 may activate gene transcription (5, 100). It has been suggested that DAX-1 represses adrenal stem cell differentiation during organ development so that a pool of progenitor stem cells can be expanded before these cells differentiate into mature steroidogenic cells. Loss of DAX-1 function, would lead to premature differentiation of progenitor cells into mature cells before expansion of cell number takes place, resulting in a transient overactivity of the gland followed by adrenal hypoplasia.

To date, more than 200 mutations of the DAX1 gene have been reported (www.hgmd.cf.ac.uk). These include large and small deletions, insertions, missense, nonsense, frameshift and splice site mutations (93, 106-111). Most missense mutations tend to cluster within the C-terminal region of the DAX-1 gene, indicating the essential role of the ligand-binding domain for the biological function of DAX1 protein (112). Gross deletions usually occur as a continuous gene deletion including the genes of glycerol kinase (GK) and Duchene muscular dystrophy (DMD). Of note, some of the patients with the contiguous gene syndrome also present with mental retardation.

DAX1 mutations have been detected in 58% of males with primary adrenal insufficiency of unknown etiology, in which common causes of adrenal failure, such as 21-hydroxylase deficiency, ALD or autoimmune disease had been excluded (93). A family history of AI (or unexplained death) or hypogonadism in male relatives is highly suggestive of X-linked AHC. Of note, positive adrenal (21-hydroxylase) antibodies and normal adrenal imaging have been recently reported in a male patient presenting with adrenal insufficiency who had a DAX-1 mutation (113). Two thirds of the patients have point mutations. Small deletions and insertions causing frameshift mutations, as well as nonsense mutations are mutations scattered throughout exons 1 and 2, whereas missense mutations are detected in exon 2 (encoding the putative ligand binding domain in the carboxyl-end of the protein).

It has been estimated that isolated and contiguous NR0B1 gene deletions account for 22 and 5% of all NR0B1 mutations, respectively. Mental retardation (MR) associated with AHC cannot be explained with GK deficiency or DMD in every case. Deletions extending to the IL1RAPL1 gene have been shown to be responsible for MR in several cases. Moreover, female carriers of NR0B1, as well as of GK or DMD mutations are at risk of developing symptoms, due to non-random X inactivation. Furthermore, in case of a contiguous gene deletion, the manifestation of the symptoms depends on the pattern of X inactivation in different tissues. Multiplex ligation-dependent probe amplification (MLPA) analysis is a valuable tool to detect NR0B1 and contiguous gene deletions in patients with AHC, showing a good genotype-phenotype correlation. It is especially helpful for the detection of IL1RAPL1 deletions causing MR, as no clinical markers for MR are available. Furthermore, MLPA has the advantage of identifying female carriers manifesting milder symptoms (114).

Patients with AHC harboring DAX1 mutations present with variable phenotypes. Typically, they develop primary adrenal failure during infancy but also later in childhood, adolescence or early adulthood. Of note, a milder form of AHC, presenting with isolated mineralocorticoid deficiency was described in an 11-yr-old boy carrying a W105C missense mutation in the amino-terminal region of DAX1 (115).

The hypogonadotropic hypogonadism may manifest as delayed puberty or pubertal arrest at about Tanner stage 3. Hypogonadotropic hypogonadism seems to involve combined hypothalamic and pituitary defects, as reflected by an impaired gonadotropin response to gonadotropin-releasing hormone (GnRH) stimulation. However, normal mini-puberty of infancy has been observed in affected boys, implying that hypothalamic-pituitary-gonadal axis defects may develop after early infancy. In addition, patients with normal puberty, gonadotropin-independent precocious puberty, central precocious puberty (5, 95, 116, 117), and impaired spermatogenesis with low inhibin B levels (5, 107, 118) have also been reported. Gonadotropin-independent precocious puberty in affected individuals may be due to a) enhanced stimulation of human melanocortin 1 receptors (MC1R) on Leydig cells by ACTH and b) an increased expression of testicular steroidogenesis activators secondary to a reduction of DAX1 repression activity. The above mechanisms may result in an increased testicular testosterone production, despite prepubertal gonadotropin levels.

Isolated infertility with normal pubertal development and normal integrity of the hypothalamic–pituitary–gonadal axis has been recently reported in a patient with adrenal insufficiency owing to a DAX1 mutation. The severely impaired spermatogenesis in this patient suggests that DAX1 mutations may lead to progressive deterioration of testicular function, independently of gonadotropin and testosterone production. The DAX1 represses aromatase production and therefore the production of estrogen in Leydig cells. It has been recently suggested that the deletion of the second exon of DAX1 may abolish the aforementioned repressor effect, resulting in aromatase overexpression and increased estrogen production. Consequently, this DAX1 dysfunction, through an indirect effect, may be able to disrupt spermatogenesis even in the presence of normal testosterone concentrations (119). Hence, semen preservation should be offered to young men with DAX1 mutations (120). Patients with oligo- or azoospermia usually fail to respond to gonadotropin treatment. Frapsauce et al reported a unique case of an infertile azoospermic patient harboring a nonsense mutation in DAX1, who was treated with FSH/hCG for 20 months and fathered a healthy boy following testicular sperm extraction-intracytoplasmic sperm injection (TESE-ICSI) (100, 121).There is no clear phenotype – genotype correlation, and the phenotypes are heterogeneous even within families, with respect to the age of onset of adrenal insufficiency, the severity of the disease and the occurrence (or not) of hypogonadotropic hypogonadism (95, 122-126). It is noteworthy, however, that adult-onset adrenal insufficiency and hypogonadotrophic hypogonadism have been linked to eight DAX1 mutations (127, 128). Interestingly, a novel non-sense p.Gln208X mutation in the amino terminal domain of the DAX-1 gene has been associated with both precocious puberty and hypogonadotropic hypogonadism in different members of a large pedigree, who had all presented with adrenal manifestations at different ages (129). This heterogeneity within families may be explained by the unique structure of the DAX-1 gene. It is also indicative of the presence of modifier genes or environmental effects on the expression of clinical manifestations (94, 130, 131). Although this is an X-linked condition, females carrying homozygous or heterozygous mutations may present with isolated hypogonadotropic hypogonadism or extreme pubertal delay, respectively. Moreover, adrenal insufficiency, moderate developmental delay and mild muscular dystrophy was reported in a girl with deletion at Xp21.2 on the maternal chromosome and skewed X inactivation (5, 108, 132-134).

Other phenotypic features such as attention deficit disorder, short stature and growth hormone deficiency have been noted in a few patients (135, 136). Inappropriate tall stature and renal ectopy associated with a DAX-1 missense mutation was reported in a single case (137). Macrophalia in infancy may be a rare feature of X-linked AHC (31). Hepatic iron deposition was documented in a male infant presenting with adrenal insufficiency as part of Xp21 deletion (138).

It is worth noting that DAX1 has anti-testis properties and antagonizes SRY (sex-determining gene region of the Y chromosome) action, required for male sex determination. NR0B1 locus duplications have been associated with 46,XY DSD/testicular dysgenesis (100).

Congenital Adrenal Hypoplasia Due to SF1 Mutations

The steroidogenic factor 1 (SF1) protein, encoded by the nuclear receptor subfamily 5 group A member 1 (NR5A1) gene, is also an orphan member of the nuclear receptor family. It was first recognized in 1992 as an element that regulates the proximal promoter region of the cytochrome p450 21-hydroxylase enzyme (139). The NR5A1 gene is located on chromosome 9q33 and encodes a protein of 461 amino acids, which is expressed in the adrenal gland, gonads, hypothalamus, anterior pituitary and spleen during development and postnatal life (140, 141). SF1 is considered the main regulator of enzymes involved in adrenal and gonadal steroidogenesis (142, 143). It is essential not only for adrenal and gonadal development and sex differentiation, but also for CNS function and metabolic homeostasis (144, 145). Among others, SF1 regulates the expression of luteinizing hormone/choriogonadotropin receptors (LHCGR), StAR, CYP11A1, and CYP17A1 in Leydig cells, SRY and SOX9 (testis-determining genes), anti-Müllerian hormone (AMH) and its receptor AMHR2 in Sertoli cells, insulin-like peptide 3 (INSL3), which is involved in testicular descent, and T-cell leukemia homeobox-11 (HOX11-TLX1), a transcription factor essential for spleen development (146, 147). SF1 expression in the hypothalamus and pituitary gland contributes to the differentiation of pituitary primordial cells into gonadotrophs (140).

CLINICAL CASES AND MUTATIONAL ANALYSIS

Targeted deletion of NR5A1 gene in mice resulted in adrenal and testicular agenesis, retained Mullerian structures and partial hypogonadotropic hypogonadism in males, as well as hyposplenism and late onset obesity (141, 144, 148-150). In the adrenals, SF1 represses the CYP11B2 (aldosterone synthase) gene (151) and facilitates CYP17 (cytochrome P450 family 17) transcription under the control of ACTH (152).

To date, more than 100 pathogenic SF1 mutations have been reported (153). A genotype-phenotype correlation cannot be observed and diverse clinical presentations even among family members carrying the same mutation may be attributed to incomplete penetrance, pathogenic variants in other testis/ovarian-determining genes, polymorphisms, environmental and epigenetic factors. The first mutation was detected in a patient with adrenal failure and complete 46,XY sex reversal, who presented during the first weeks of life with low circulating cortisol, low aldosterone and high ACTH concentrations. Although the karyotype of the patient was 46,XY, normal

Müllerian structures and streak-like gonads containing poorly differentiated seminiferous tubules and connective tissue were detected (154). The patient had a *de novo*, heterozygous loss-of-function missense mutation (p.G35E) causing substitution of glycine at amino acid 35 by glutamate in the DNA-binding domain of the protein, abolishing its DNA-binding activity. Pituitary gonadotropins responded to GnRH stimulation, but testosterone did not respond to exogenous hCG administration, suggesting defective gonadal function. After introduction of estrogen and progesterone, the uterus grew and regular menstruation ensued. This case was the first to indicate that SF1 is essential for sex determination, steroidogenesis and reproduction.

The second patient was a phenotypically female infant, who presented with hypoglycemic convulsions, progressive hypotonia, weight loss, hyponatremia and hypokalemia. Genetic testing revealed homozygosity for the p.R92Q mutation, whilst her consanguineous parents and her sister were heterozygous for the mutation. Although DHEA concentrations were detectable, 17-hydroxyprogesterone concentrations were low. The abdominal CT scan demonstrated left adrenal hypoplasia and right adrenal agenesis. The patient's karyotype was 46,XY and a uterus was seen on pelvic ultrasound and confirmed by magnetic resonance imaging (155).

A phenotypically and genotypically normal girl (46,XX), with adrenal failure and no apparent defect in ovarian maturation was described in 2000 (156). The patient had a heterozygous G to T transversion in exon 4 of the NR5A1 gene, resulting in the missense p.R255L mutation. The inability of the mutant NR5A1/SF1 to bind canonical DNA sequences offered a possible explanation for the failure of the mutant protein to transactivate target genes. This was the first report of a mutation in the NR5A1 gene in a genotypically female patient, suggesting that SF1 is not necessary for female gonadal development, although it plays a crucial role in adrenal gland formation in both sexes.

Since then, only two cases of isolated adrenal insufficiency (AI) have been reported (31, 157). One of them, a 46 XX female, with early-onset primary AI, was homozygous for the p.R92Q mutation, previously associated with 46XY DSD (31).

In contrast, there have been several reports of various types of NR5A1 mutations (including missense, nonsense, and frameshift), affecting the DNA binding domain of the protein in individuals with different forms of 46,XY disorders of sex differentiation (DSD) and associated adrenal insufficiency (93, 158, 159) or without an adrenal phenotype (160-165). Pathogenic NR5A1 variants have been identified in 10-20% of all 46 XY DSD cases. They usually arise *de novo*, but can be maternally inherited in a sex-limited dominant manner in 30% of cases (100). Phenotypic features include: female or ambiguous genitalia with inguinal or labial testes and remnant or no Müllerian structures (present in 24% of patients) (147), clitoral hypertrophy, labioscrotal folds, labioscrotal testes, bilateral anorchia (166), micropenis and hypospadias (164, 167-169). Biochemical evidence of hypogonadotrophic hypogonadism along with testicular dysfunction and borderline adrenal dysfunction was observed in a case of 46XY DSD dizygotic twins, harbouring a heterozygous frameshift mutation in the C-terminal region of NR5A1 (170). Of note, there are several reports of affected individuals, presenting with female external genitalia in the neonatal period followed by spontaneous and progressive virilization in adolescence. However, FSH levels remained persistently elevated in all cases, suggesting that Leydig cell function may be preserved while Sertoli cells are more severely affected (171).

Splenic anomalies may be an additional feature of patients with 46 XY DSD harboring SF1 mutations. A homozygous SF1 mutation, R103Q was found in a 46 XY patient presenting with complete sex reversal, asplenia and mildly elevated ACTH levels but no evidence of an AI. The SF1 R103Q mutant was shown to decrease the transcriptional activity of the spleen development gene TLX1, and impair the transcriptional activation of steroidogenic enzymes, without disrupting the synergistic effect of SF-1 with either SRY or SOX9 (146). Moreover, the *de novo* heterozygous deletion of 143 bp (c.616_758del) was identified in 6-week-old 46,XY female with complete sex reversal, AI and splenic hypoplasia. Finally, polysplenia was reported in a phenotypically female 46,XY-DSD patient carrying a heterozygous SF1 mutation, p.Tyr409* in the ligand-binding domain. The same mutation was found in her father, who had asplenia and hypospadias (172).

The phenotypic spectrum of SF1 mutations has been further expanded to include 46,XX ovotesticular/testicular DSD associated with the p.Arg92Trp and p.Arg92Gln variants. Affected patients may present with ambiguous genitalia with a uterus/hemi-uterus or as phenotypic males with testes (173-175). It has been suggested that p.Arg92Trp mutation results in downregulation of the pro-ovarian Wnt4/β-catenin pathways, thus leading to increased expression of SOX9 and other pro-testis genes at the gonadal level, switching organ fate from ovary to testis.

In addition, missense changes, in-frame deletions, frameshift, and nonsense mutations in NR5A1 have been found in 46,XX females with isolated ovarian insufficiency and account for about 1.4–1.6% of women presenting with sporadic primary ovarian insufficiency (POI) of unknown origin (100, 165, 176). Mothers or sisters who are heterozygous carriers may experience menstrual irregularities, decreased ovarian reserve, early menopause and rarely absence of puberty (100, 175).

Furthermore, NR5A1 mutations mostly located in the hinge region (100) may be found in 1.6-4% of men with otherwise unexplained severe impairment in spermatogenesis (177, 178). Gonadoblastoma and Germ Cell Neoplasia *In Situ* (GCNIS) have also been reported (179). Recent data indicate, that patients carrying NR5A1 mutations show distinct testicular histological features, i.e. reduced number of thin seminiferous tubules and focal aggregations of Leydig cells, containing cytoplasmic lipid droplets. Hence, testicular histology may be useful in identifying NR5A1 mutations in 46,XY patients with DSD before puberty. More recently, studies in mice indicate that lipid accumulation in the Leydig cells in 46 XY DSD is associated with decreased expression of StAR and CYP11A1, resulting in an increase in unmetabolized cholesterol (180, 181).

The above data indicate that SF1 mutations may lead to a wide range of endocrine phenotypes, which are only rarely related to adrenal insufficiency.

To date, microdeletions of chromosome 9q33.3, involving the NR5A1 gene have been reported in three patients with DSD. The first is a 3 Mb deletion in a 46,XY female, presenting with clinical features of Genitopatellar syndrome, developmental delay and ovotestes (182). The second is a unique 970kb microdeletion encompassing NR5A1, and resulting in XY sex reversal with clitoromegaly, neonatal male testosterone and AMH levels and a normal urine steroid profile (183). The third is a de novo 1.54 Mb microdeletion in a patient with 46,XY DSD and mild developmental delay (184).

Recently, a novel heterozygous p.Cys65Tyr mutation in NR5A1 gene has been identified in three 46,XY siblings of a Brazilian family, who presented with ambiguous genitalia without Müllerian derivatives and apparently normal Leydig function after birth and at puberty, respectively. Their mother, who reported symptoms suggestive of primary ovarian insufficiency was also heterozygous for this mutation. Basal ACTH and cortisol concentrations were slightly elevated and normal, respectively, in all three patients. After 1 mcg ACTH stimulation test, only the older sibling showed subnormal cortisol response. The above data indicate that NR5A1 analysis should be performed in 46,XY DSD patients with normal testosterone concentrations without AR mutations. Furthermore, a long-term follow-up for adrenal function is important for those patients (185).

IMAGe Syndrome

CLINICAL FEATURES AND LABORATORY FINDINGS

The acronym IMAGe indicates the presence of Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal *hypoplasia congenita*, and Genital anomalies (10, 186).

The life-threatening components of the adrenal insufficiency in this syndrome generally develop in the neonatal period. It usually manifests in the first few days of life with adrenal crises and may be the first sign of the disease. In some patients it may present later in childhood with failure to thrive and recurrent vomiting or in early adulthood. Hypoaldosteronism without evidence of glucocorticoid deficiency was also reported in one case (187). On imaging studies, the adrenal glands may appear small or normal in size. Radiologic identification of metaphyseal dysplasia is often crucial for the diagnosis, but this could be very mild and identifiable only in late infancy or in childhood and then progress with age. Additional radiographic features may include: epiphyseal dysplasia, mesomelia, osteopenia, gracile long bones, and delayed bone age (188).

A more precocious sign, i.e. delayed endochondral ossification associated with osteopenia, hypercalcemia, and/or hypercalciuria of unclear aetiology and of variable degree can be encountered in patients with this syndrome. Abnormalities in serum calcium concentrations may be present at birth and resolve later in infancy. Soft tissue calcifications have been occasionally reported (188).

Another endocrine involvement in these patients is GH deficiency and early substitution therapy could improve linear growth.

Specific dysmorphic craniofacial features in IMAGe syndrome include nonspecific signs, such as prominent forehead, macrocephaly, low-set ears, ear dysplasia, flat nasal bridge, and short nose, short arms and legs. micrognathia or retrognathia, cleft palate or cleft uvula, craniosynostosis, short palpebral fissures, smooth philtrum, microglossia, arachnodactyly, and bilateral 2–3 toe syndactyly (187-189).

Genital abnormalities seem to be confined to males and include micropenis, undescended testes, chordee and hypospadias of variable severity. Two female patients were reported to give birth to children. Labor may be complicated by cephalopelvic disproportion.

Additional features associated with the syndrome include:

- Skeletal abnormalities: progressive and severe scoliosis with onset before age five years, ovoid-shaped vertebral bodies, short first metatarsals, hallux valgus, hip dysplasia, fractures of the humerus and tibia present at birth
- Renal abnormalities: hydronephrosis, hypercalciuria-associated nephrocalcinosis
- Other: oligohydramnios (187-188).

GENETICS

IMAGe syndrome (OMIM 614732) is exclusively related to mutations of CDKN1C gene [cyclin-dependent kinase inhibitor 1C (p57, Kip2)] (190). Notably, familial analysis demonstrated *de novo* mutations or an imprinted mode of inheritance, exclusively with maternal transmission of the mutation. The responsible gene lies on 11p15, contains three exons and encodes p57 (KIP2), a potent tight-binding inhibitor of several G1 cyclin/Cdk complexes (cyclin E-CDK2, cyclin D2-CDK4, and cyclin A-CDK2). It is a negative regulator of cell proliferation, playing a role in the maintenance of the non-proliferative state throughout life, probably acting as a tumour suppressor gene. CDKN1C is expressed in the placenta, heart, brain, lung, skeletal muscle, kidney, pancreas, testis, eye, and in the subcapsular or developing definitive zone of the adrenal gland. To date, clinical manifestations suggestive of IMAGe syndrome have been described in 28 individuals. Six missense mutations have been documented in 17 out of 28 patients, all of which occur in the PCNA-binding domain in the carboxy-terminal region of CDKN1C (186, 188). Recently, Hamajima et al (191) demonstrated that the IMAGe-associated mutations cause a dramatically increased stability of the CDKN1C proteins, which probably results in a functional gain of growth inhibition properties. Further studies have shown that mutations in the PCNA-binding site of CDKN1C lead to a block in the G1 phase and impaired S-phase entry resulting in decreased cell proliferation (192). In contrast, loss-of-function CDKN1C mutations are associated with the Beckwith-Wiedemann syndrome (BWS), which represents an additional imprinting disorder with a mirror phenotype of IMAGe syndrome. BWS mutations are not clustered within a single domain and promote cell proliferation (186).

A novel CDKN1C mutation (c.842G>T, p. R281I) that did not entirely abrogate proliferating cell nuclear antigen binding has been recently associated with features of IMAGe syndrome, however, without adrenal insufficiency or metaphyseal dysplasia, but with early-adulthood-onset diabetes (189). A novel missense variant of CDKN1C (c.836G>[G;T], p.Arg279Leu) was also identified in a familial case of Russell Silver syndrome (193). Of note, both mutations were located within the PCNA-binding site of CDKN1C gene and were maternally inherited, thus producing phenotypic overlaps of IMAGe syndrome.

MIRAGE Syndrome

MIRAGE syndrome (OMIM 617053) is a rare form of syndromic adrenal hypoplasia, associated with high mortality rates during the first years of life. First described in 2016, MIRAGE stands for Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes and Enteropathy. The genetic basis of the syndrome has been linked to germline, mostly *de novo*, gain-of-function, heterozygous mutations in SAMD9 (sterile alpha motif domain-containing protein 9) gene. Homozygous loss-of-function SAMD9 mutations have been shown to result in normophosphatemic familial tumoral calcinosis (194).

GENETICS

SAMD9 gene resides on the long arm of chromosome 7 (7q21.2) and encodes a 1,589-amino acid protein that regulates cell proliferation and exhibits wide tissue expression, including in adrenal glands, colon, bone marrow, liver, immune system, lung, and testis (195, 196). SAMD9 facilitates endosome fusion and is likely to function as a growth repressor. It has been shown that expression of the wild-type SAMD9 resulted in decreased cell proliferation, whereas expression of mutants resulted in profound growth inhibition. At the cellular level, patient-derived fibroblasts displayed increased size of early endosomes, intracellular accumulation of giant vesicles and decreased plasma membrane epidermal growth factor receptor (EGFR) expression, likely due to defects in receptor recycling (194).

CLINICAL FEATURES AND LABORATORY FINDINGS

To date, heterozygous SAMD9 mutations associated with two or more components of MIRAGE syndrome have been reported in 24 patients (194-198).

Genital abnormalities may range from micropenis, cryptorchidism and hypospadias to ambiguous genitalia and completely feminized external genitalia in 46XY affected individuals. Of note, only 25% of reported cases were females, indicating that the syndrome may be underdiagnosed in girls. Histologically, the ovaries were markedly hypoplastic and dysgenetic in two patients, containing few primordial follicles (194, 195, 199).

Neonatal severe adrenal insufficiency is a common manifestation. Adrenal imaging may reveal hypoplasia or even absence of adrenal glands. Histologic studies have shown very small, highly disorganized, dysgenetic adrenal glands (194,195).

Thrombocytopenia and/or anemia, requiring transfusions may manifest within the first week of life, however spontaneous resolution has been reported in many cases (196, 197).

Myelodysplastic syndrome (MDS) associated with monosomy 7 or monosomy 7q was reported in 6 out of 24 MIRAGE-affected individuals. The researchers demonstrated that the preferential loss of the allele harboring the gain-of-function SAMD9 mutation, through the development of monosomy 7 (–7), deletions of 7q (7q–) or secondary somatic loss-of-function provide a survival advantage in affected hematopoietic cells. This is an example of an “adaptation by aneuploidy” mechanism, relieving the growth-restricting effect of the mutated gene, however at the expense of an increased risk for MDS (194, 195, 197, 199). Interestingly, two patients harboring two *de novo* SAMD9 mutations on the same allele, one activating SAMD9 mutation, and one second-site reversion nonsense mutation in the haematopoietic cells, exhibited no haematologic manifestations (198).

Additional features of the disorder include (194-196, 198-199):

- Moderate-to-severe growth restriction during both the prenatal and postnatal periods, premature delivery, fetal death
- Severe bacterial and viral infections, including sepsis, meningitis, and fungal infections thymus hypoplasia
- Chronic diarrhea with colonic dilation, feeding difficulties frequently requiring surgical feeding tube placement
- Dysmorphic features: frontal bossing, low-set ears, ptosis, down-turned corners of the mouth, round face, sparse hair, small feet and hands, tapered fingers, short phalanges, abnormal nails
- Bronchopulmonary dysplasia
- Neurologic abnormalities: dysautonomia hypolacrima, hyperhidrosis and blood pressure

dysregulation, syringomyelia, hypoplastic pons and cerebellum, hydrocephalus, bilateral auditory neuropathy, developmental delay

- Skeletal abnormalities: scoliosis, joint contracture in wrists and ankles
- Renal defects: renal tubular acidosis, glucosuria, defects in phosphate reabsorption and urinary concentration
- Apneas
- Reduced body fat

The majority of patients reported to date died within the first two years of life.

Familial Steroid-Resistant Nephrotic Syndrome with Adrenal Insufficiency

Most recently, in 2017, three study groups unraveled concurrently the genetic basis of a syndrome encompassing steroid-resistant nephrotic syndrome (SRNS) and primary adrenal insufficiency (PAI). Using whole exome sequencing analysis on patient cohorts with PAI or SRNS the researchers identified novel genetic mutations in the gene encoding sphingosine-1-phosphate (S1P) lyase 1 (SGPL1), located on chromosome 10q22.1 (200-202).

GENETICS

SGPL1 is an important endoplasmic reticulum (ER) enzyme that catalyzes the irreversible cleavage of the lipid molecule S1P to trans-2-hexadecenal and ethanolamine phosphate. S1P exhibits extracellular actions by activating a family of five differentially expressed extracellular G-protein-coupled receptors (G protein-coupled receptors (S1PRs) and intracellular functions via S1PR-independent mechanisms as well. S1P regulates multiple biological processes including cell migration, differentiation, angiogenesis, vascular maturation, cardiac development and immunity (200-202).

A total of 13 SGPL1 variants in 14 families have been reported so far (203). These were recessive loss-of-function mutations (homozygous or compound heterozygous) resulting in decreased or absent SGPL1 expression and/or enzyme activity, subcellular mis-localization of SGPL1 and altered levels of sphingolipid metabolism intermediates (200-202).

The pathogenesis of the syndrome may involve an excess of intracellular S1P, an imbalance of other sphingoid bases, S1P signaling through the S1P receptors or a lack of phosphoethanolamine production (201, 202).

SGPL1 is expressed in several mammalian tissues, among which in the adrenals and testes. Sgpl1–/– mice were shown to have impaired testicular and ovarian steroidogenesis and infertility. Recent studies have documented several histologic abnormalities in the adrenal glands of Sgpl1–/– mice, including compromised cortical zonation with less definition between *zona glomerulosa* (ZG) and *zona fasciculata* (ZF) and between ZF and X-zone as well as loss of vacuolization in the ZF. Furthermore, Sgpl1–/– adrenals displayed decreased cytochrome P450 side-chain cleavage (CYP11A1), reflecting impaired steroidogenesis. These data may indicate the potential role of SGPL1 on adrenal development (200).

CLINICAL FEATURES AND LABORATORY FINDINGS

Human SGPL1 mutations cause a multisystemic disorder, with the main components being PAI and SRNS (200-204).

PAI is manifested in almost all cases, usually during infancy and less frequently during childhood or later. Most patients exhibit an FDG phenotype, necessitating treatment with hydrocortisone only. However, in some cases additional mineralocorticoid treatment may be required. Of note, markedly low adrenal androgen levels were reported in one affected postpubertal patient. Adrenal imaging (U/S or MRI) performed in some cases revealed i) normal findings ii) calcifications in the adrenals and iii) bilateral enlarged adrenal glands in one case (200-202).

Most affected patients suffer from nephrotic syndrome (NS), which is typically manifested as congenital NS (clinical symptoms occurring during the 3 months after birth) or within the first year of life and is steroid-resistant, leading rapidly to end-stage renal disease requiring renal transplantation. Histologic examinations have shown mainly focal segmental glomerulosclerosis, but diffuse mesangial sclerosis and foci of calcification have also been reported (200-203).

The phenotypic spectrum of this syndrome is broad and associated features other than SRNS and PAI may include (200-204):

- Adrenal calcifications
- Dermatologic abnormalities: ichthyosis, acanthosis, hyperpigmentation, scaly lesions, calcinosis cutis
- Neurologic abnormalities: developmental delay, ptosis, strabismus, abnormal gait, ataxia, sensorineural deafness, seizures, microcephaly, cortical, cerebellar or corpus callosum hypoplasia, peripheral neuropathy, contrast enhancement of cerebellar structures and bilateral globus pallidus, medial thalamic nucleus and central pons, FLAIR-hyperintensity in hippocampus and brainstem.
- Ophthalmologic abnormalities: “salt and pepper” retinopathy, amblyopia
- Immunodeficiencies: lymphopenia, deficiency of cellular immunity, multiple bacterial infections, hypogammaglobulinemia, thrombocytopenia and anemia
- Genital abnormalities: micropenis, cryptorchidism, hypergonadotropic hypogonadism, microorchidism associated with low serum anti-Müllerian hormone
- Skeletal abnormalities: craniotabes, rachitic rosary, asymmetric skull, scoliosis, short stature
- Hypothyroidism
- Muscular hypotonia
- Fetal demise, fetal hydrops
- Other: facial dysmorphism (microstomia, hypertelorism, down-slanting palpebral fissures, epicanthus, dysplastic ears), hypocalcemia, mild dilated cardiomyopathy, intestinal malrotation, capillary leak syndrome.

Lovric et al have proposed the term Nephrotic syndrome, type 14 (NPHS14) to describe this syndromic form of SRNS associated with SGPL1 gene mutations (OMIM: 617575) (201).

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Bookshelf ID: NBK279132 PMID: 25905355