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PATOLOGÍA ADRENAL

Genetic disorders of primary adrenal insufficiency beyond CAH

Trastornos genéticos de la insuficiencia suprarrenal primaria más allá de la HSC

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Abstract

Primary adrenal insufficiency (PAI) is caused by disorders of the adrenal cortex that lead to cortisol deficiency. Underlying genetic defects may manifest with an adrenal phenotype only or affect other organ systems. Genetic causes of PAI may be sub-grouped into disorders of steroidogenesis (mainly congenital adrenal hyperplasia), adrenal dysgenesis, familial glucocorticoid deficiency (FGD), and metabolic and autoimmune disorders. Current genetic work-up of PAI yields a specific diagnosis in up to 80% of cases. The latest gene defects discovered in syndromic cases of PAI include variants of *CDKN1C* and *POLE1* in IMAGe syndrome, *SAMD9* in MIRAGE syndrome and variants of *SPGL1* in a new sphingolipidosis. The latest gene defects manifesting as FGD were found in the mitochondrial gene network regulating reactive oxygen species (*NNT*, *TXNRD2*). Knowing the exact genetic diagnosis in a patient with PAI is important to provide optimal care and for genetic counseling. It forms the basis for future gene therapeutic options and cell replacement strategies.

Introduction

Primary adrenal insufficiency (PAI) is defined by cortisol deficiency in humans due to disorders of the adrenal cortex affecting its production. Cortisol is produced in the zona fasciculata (zF, middle zone) of the adrenal cortex. This glucocorticosteroid hormone is responsible for the acute and chronic stress response and thus the regulation and maintenance of the energy homeostasis of the human body. Other steroid hormones produced by the adrenal cortex are mineralocorticoids in the zona glomerulosa (zG) for maintaining water and electrolyte balance, and adrenal androgens in the zona reticularis (zR), which contribute to the sex steroid pool [(1)]. Cortisol production of the adrenal cortex is controlled by the hypothalamic-pituitary-adrenal (HPA) axis. Essential players comprised in this axis are the hormones corticotropin releasing hormone (CRH), adrenocorticotropic hormone ACTH, the ACTH receptor (*MC2R*), as well as the GPCR/cAMP/MAPK signaling pathway and cortisol. Cortisol then acts predominantly on the glucocorticoid (GC) receptor *NR3C1* to exert its action on multiple biological processes and organs. The HPA axis also co-regulates adrenal androgen production, while mineralocorticoid production (mainly aldosterone) is controlled by the renin-angiotensin-aldosterone system.

Genetic variants causing PAI either disrupt cortisol production and steroidogenesis only leading to **isolated PAI** or they cause additional organ malfunctions as part of a syndrome in **syndromic PAI**. In isolated PAI, genetic disorders may affect the structure and function of the adrenal cortex or adrenal steroidogenesis specifically, but often also lead to overall disturbances of steroidogenesis affecting other steroid organs (mainly the gonads or the placenta). This can then result in different disorders of sex development (DSD), as steroid hormone biosynthesis, regulation and metabolism rely on a common gene network. Nevertheless, cell- and tissue-specific expression and regulation of steroidogenic genes leads to organ-specific steroid production. Genetic variants in core genes of steroid hormone biosynthesis may therefore be recognized by characteristic clinical phenotypes and changes in steroid profiles assessed in biosamples such as plasma and urine. However,

considerable overlap exists so that a characteristic clinical and biochemical profile may be caused by variants in more than one gene, and different variants in one gene may manifest as phenotypically variable.

Although syndromic forms of PAI seem easier to recognize through their broader range of typically involved organ systems, this remains just a theory in many cases. Syndromes with PAI can manifest similar, oligosymptomatic or atypical mainly because the typical spectrum may only develop over time or simply because the phenotype is only recognized when searched for.

However, disorders leading to PAI may not only be grouped according to whether they affect just the adrenal structure and function or lead to defects in other organ systems. They may also be characterized by their suggested molecular disease mechanism. Table 1 gives an overview of all monogenetic disorders causing PAI reported in the literature to date.

PAI often manifests (very) early in life or even goes undiagnosed when embryonic or neonatal lethal, although late-onset manifestation in adulthood is also seen. Clinical signs of adrenal insufficiency are non-specific, but with severe stress such as major illness, trauma or surgery an acute adrenal crisis may be triggered. Signs and symptoms of an acute crisis include abdominal pain, fever, hypoglycemic seizures, weakness, apathy, nausea, vomiting, anorexia, hyponatremia, hypochloremic acidemia, hyperkalemia, hypotension, shock, cardiovascular collapse, and sudden death.

Milestones in medicine concerning PAI were the first clinical description of a patient with PAI by Thomas Addison in 1849, the first description of a patient with congenital adrenal hyperplasia (CAH) by Luigi De Crecchio in 1865, the isolation of cortisol from adrenal extracts by Edward Calvin Kendall and its synthesis for medical use by Lewis H. Sarett in 1946, and the identification of the first genes causing CAH (*CYP21A2*) by Perrin White in 1984 and familial glucocorticoid deficiency (*MC2R*) by Adrian J.L. Clark and Constantine Tsigos in 1993.

Several comprehensive reviews have recently been published on the topic of genetic disorders of the adrenal cortex and steroidogenesis [2-11]. This update summarizes the genetic causes of PAI with an emphasis on the most recent findings and a perspective on current diagnostic yield and future therapeutic options.

Update on more recent findings on the topic of monogenetic disorders causing PAI

In the group of **steroid biosynthetic defects** (Table 1), we have learned from affected persons that autosomal recessive gene variants coding for enzymes and cofactors involved in adrenal steroidogenesis (and beyond) may manifest with variable phenotype. This has long been known for variants in *CYP21A2*, where loss of function mutations cause classic CAH and milder enzyme defects lead to non-classic, late-onset CAH [10]. Likewise, less severe autosomal recessive genetic variants in *STAR* [12] and *CYP11A1* [13] have been identified in patients with an adrenal phenotype only mimicking familial GC deficiency (FGD) [14] and not typical lipoid CAH, in which adrenal and gonadal steroidogenesis is affected leading to PAI and 46,XY DSD [15]. Similarly, different variants in P450 oxidoreductase can manifest with a vast range of phenotypes ranging from the severest Antley Bixler skeletal and genital malformation syndrome to moderate forms with a CAH phenotype, and to mild forms overlapping with polycystic ovary syndrome in females or lyase deficiency syndrome in males [16-18].

In the group of **structural developmental defects** of the adrenal cortex, X-linked adrenal hypoplasia congenita due to pathogenic variants in the *DAX1/NROB1* gene remains the most frequently identified genetic defect in males with PAI [8]. By contrast, genetic variants in *SF1/NR5A1* are rarely identified in PAI, but they typically manifest with a broad range of DSDs in both sexes [19]. Conversely, very rare syndromic forms of PAI affecting adrenal development and function and affecting fetal growth have been identified more recently through the efforts of next-generation genetic work-up. These include the IMAGe and MIRAGE syndromes (Table 1).

In **IMAGe syndrome** specific heterozygous gain-of-function mutations in the *CDKN1C* (cyclin-dependent kinase inhibitor 1C) gene were found in patients manifesting with intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies [20]. In addition, biallelic *POLE* mutations causing DNA polymerase epsilon deficiency with a variable degree of immunodeficiency were discovered in another 15 patients of 12 families with IMAGe syndrome [21]. POLε is one of the leading polymerases for DNA replication essential for the correct transmission of genetic information. To date, all CDKN1C mutations identified in IMAGe syndrome cluster in the proliferating cell nuclear antigen (PCNA) binding domain. At the initiation of replication, PCNA loads with POLε, and thus the phenotypic overlap of CDKN1C with POLE-associated IMAGe syndrome suggests a mechanistic link [21]. Together with *MCM4* mutations, *CDKN1C* and *POLE* mutations share a common profile of PAI including growth restriction and immunodeficiency due to impaired replisome function [21, 22].

MIRAGE syndrome is characterized by myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, enteropathy

Table 1. Reported monogenetic causes of primary adrenal insufficiency and associated phenotype [2].

	Disorder	Gene	OMIM	Associated clinical features in addition to PAI
Defects of steroid biosynthesis *(e.g. congenital adrenal hyperplasia)*	Congenital lipoid adrenal hyperplasia (LCAH)	*StAR*	201710	46,XY DSD, gonadal insufficiency
	P450 side chain cleavage syndrome (CAH)	*CYP11A1*	118485	46,XY DSD, gonadal insufficiency
	3β-hydroxysteroid dehydrogenase deficiency (CAH)	*HSD3B2*	201810	46,XY DSD and 46,XX DSD, gonadal insufficiency
	21-hydroxylase deficiency (CAH)	*CYP21A2*	201910	46,XX DSD, androgen excess syndrome, testicular adrenal rest tumors
	11β-hydroxylase deficiency (CAH)	*CYP11B1*	202010	46,XX DSD, hypertension, androgen excess syndrome
	17-hydroxylase deficiency (CAH)	*CYP17A1*	202110	46,XY DSD, hypertension, gonadal insufficiency
	P450 oxidoreductase deficiency (CAH)	*POR*	613571	46,XY DSD, 46,XX DSD, gonadal insufficiency, Antley-Bixler skeletal malformation syndrome; changes in drug metabolism
	Steroidogenic factor 1 deficiency	*NR5A1 (SF1)*	184757	46, XY DSD, gonadal insufficiency
	Aldosterone synthase deficiency	*CYP11B2*	124080	Isolated mineralocorticoid deficiency
Adrenal dysgenesis *(e.g. hypoplasia, agenesis)*	X-linked adrenal hypoplasia congenita (AHC)	*NROB1 (DAX1)*	300200	Hypogonadotropic hypogonadism, in some cases gonadotropin independent precocious puberty
	IMAGe syndrome	*CDKN1C POLE1*	614732 618336	IUGR, bone disorders and anomalies, genital anomalies, hypercalcemia, dysmorphic facial features, immunodeficiency
	MIRAGE syndrome	*SAMD9*	617053	Myelodysplasia, infections, restriction of growth, genital anomalies, enteropathy
	SERKAL syndrome	*WNT4*	611812	46,XX DSD, IUGR, cleft lip/palate, dysplastic kidneys and lungs, heart defects, diaphragmatic hernia, intestinal malrotation
	Pallister-Hall syndrome	*GLI3*	165240	Hypothalamic hamartomas, mesoaxial and postaxial polydactyly, bifid epiglottis, imperforate anus, genitourinary anomalies
	Meckel syndrome	*MKS1*	249000	Cystic renal disease, CNS malformation - occipital encephalocele, polydactyly, hepatic abnormalities
	Pena-Shokeir syndrome	*DOK7, RAPSN*	208150	Arthrogryposis, facial anomalies, IUGR, camptodactyly, fetal akinesia, polyhydramnion, pulmonary hypoplasia, cardial defects, intestinal malrotation
	Pseudotrisomy 13		264480	Holoprosencephaly, polydactyly, craniofacial anomalies
	Hydrolethalus syndrome	*HYLS1*	236680	Hydrocephaly, micrognathia, polydactyly abnormal genitalia, congenital heart defects, respiratory organ defects
	Galloway-Mowat syndrome	*WDR73*	251300	Nephrotic syndrome, microcephaly, encephalopathy, hiatus hernia

ACTH resistance/ FGD	Familial glucocorticoid deficiency (FGD)	*MC2R MRAP*	202200 607398	Mostly normal production of mineralocorticoids, tall stature
	FGD - Deficiency of mitochondrial ROS detoxification	*NNT*	614736	Only glucocorticoid deficiency
		TXNRD2	606448	Only glucocorticoid deficiency
		GPX1		Only glucocorticoid deficiency
		PRDX3		Only glucocorticoid deficiency
FGD-like *(but more complex, syndromic)*	DNA repair defect	*MCM4*	609981	NK cell deficiency, short stature, microcephaly, recurrent viral infections, chromosomal breakage
	AAA syndrome – Triple A (Allgrove syndrome)	*AAAS*	231550	Alacrimia, achalasia, deafness, mental retardation, hyperkeratosis
Cholesterol synthesis disorders	Wolman disease	*LIPA*	278000	Xanthomatous changes in the liver, adrenal, spleen, lymph nodes, bone marrow, small intestine and thymus, diffuse punctate adrenal calcification, hepatosplenomegaly, poor weight gain, hypercholesterolemia, steatorrhea
	Smith-Lemli Opitz disease	*DHCR7*	270400	Multiple congenital malformation and mental retardation syndrome
	Abeta-lipoproteinemia	*MTP*	200100	Ataxia, retinopathy, acanthocytosis, pathologic fat absorption
	Familial hypercholesterolemia	*LDLR*	143890	Xanthomas, corneal arcus, and coronary artery disease
	Sitosterolemia (Phytosterolemia)	*ABCG5 ABCG8*	210250	Short stature, gonadal failure, xanthomas, arthritis, coronary heart disease
Peroxisomal defects	X-linked adrenoleukodystrophy	*ABCD1 ABCD2*	300100 300371 601081	Progressive neurodegeneration, dementia, progressive behavioral disturbances, vision and hearing loss, spasticity and seizures; accumulation of very long chain fatty acids
	Neonatal adrenoleukodystrophy	*PEX1*	601539	Hypotonia, seizures, diffuse encephalopathy, sensorineural hearing loss, peripheral neuropathy, mild facial dysmorphism; autosomal recessive
	Infantil Refsum disease	*PHYH, PEX7*	266500	Anosmia, retinitis pigmentosa, neuropathy, deafness, ataxia, ichthyosis
	Zellweger syndrome	*PEX1 and other PEX genes*	214100	Severe neurologic dysfunction with handicaps, craniofacial abnormalities, severe mental retardation, hepatomegaly, growth failure, stippled epiphysis, genitourinary anomalies
Mitochondrial defects	Kearns-Sayre syndrome	*mitDNA del*	530000	Progressive external ophthalmoplegia, pigmented retinopathy, cardiac conduction block, cerebellar ataxia; other endocrine pathologies
	(Combined) mitochondrial complex deficiency (Leigh syndrome)	*MRPS7*	617872	Sensorineural deafness, liver and kidney failure, hypogonadism, neuro-developmental delay. Lactic acidosis.
		NDUFAF5	612360	IUGR, brain anomalies and neurodegeneration resulting in neurodevelopmental delay, spasticity, chorea and seizures. Diaphragmatic hernia. Lactic acidosis.
		GFER	613076	Progressive myopathy with congenital cataract and developmental delay

Lysosomal defect	Sphingosine-1-phosphate lyase 1 deficiency	*SPGL1*	603723	Steroid-resistant nephrotic syndrome, optionally accompanied by ichthyosis, primary hypothyroidism, cryptorchidism, immunodeficiency and neurological defects
Autoimmune disorder	Autoimmune polyglandular syndrome type 1 (APS1, APECED)	*AIRE*	240300	Hypoparathyroidism, candidiasis, autoimmune hypergonadotropic hypogonadism, autoimmune thyroid diseases alopecia, chronic autoimmune hepatitis, pernicious anemia, vitiligo
	Autoimmune polzglandular syndrome type 2 and isolated autoimmune PAI	*HLA-DR3, DR4, CTLA4, BACH2, PTPN22, GATA3, CLEC16, MIC-A/B, NALP1, AIRE*		Autoimmune thyroid disorders, premature ovarian failure, vitiligo, pernicious anemia, type 1 diabetes and other autoimmune disorders
	Immunodeficiency 31C	*STAT1*	614162	Chronic mucocutaneous candida and other infections, polyendocrinopathy, cerebral aneurysma

and early death. In patients with MIRAGE syndrome, *SAMD9* (sterile alpha motif domain-containing protein 9) mutations have been discovered [23, 24]. *SAMD9* is involved in endosome fusion and is reported to play a role in growth factor signaling transduction. Thus, heterozygote *SAMD9* mutations seem to enhance its intrinsic endosome-fusing activity and may thereby lead to abnormal tissue development including dysgenetic and hypoplastic adrenal glands, ovaries and thymus, and result in deleterious overall growth-restricting effects and short survival. In some MIRAGE patients, longer survival seems possible through genetic escape mechanisms such as somatic mutations and progressive monosomy resulting in loss of mutated *SAMD9* effects in the bone marrow [23]. However, this may come at the cost of increased risk for myelodysplastic syndromes in the long run. Interestingly, *SAMD9* mutations were recently also found in a severely undervirilized 46,XY DSD child born SGA without PAI, but otherwise typical features of MIRAGE syndrome [25]. And another recent report of two unrelated patients carrying novel and known *SAMD9* mutations expanded the typical phenotypic spectrum by including PAI by CNS anomalies and global developmental delay, dysautonomy, hearing loss and chronic lung disease [26].

Overall, it is remarkable how few variants in genes that are critically involved in adrenal development, as revealed by basic research studies, have been identified in humans with dysgenetic, syndromic PAI [27]. One of these genes is *WNT4*. But so far a homozygous mutation in *WNT4* has been identified in only one family with the **SERKAL syndrome** (female sex reversal and dysgenesis of kidneys, adrenals, and lungs) [28]. It is therefore very likely that pathogenic variants in genes essential for adrenal development and beyond are embryonic lethal.

In the early era of genetics, first two genes causing **familial glucocorticoid deficiency** (FGD) were identified, namely mutations in the ACTH receptor (*MC2R*) and its accessory protein (*MRAP*) [29, 30]. In addition, the syndromic variant of FGD, triple A or Allgrove syndrome, was solved genetically by identifying mutations in the *AAAS* gene [31]. *AAAS* is a nucleoporin component thought to be involved in cellular stress response [32]. However, mutations in the aforementioned genes were identified in less than a third of patients with FGD. More recently, newer genetic methods discovered a novel group of genes located in the mitochondria responsible for oxidative stress homeostasis [33]. Very quickly, many mutations in the nicotinamide nucleotide transhydrogenase (NNT) gene of the energy transfer system of the respiratory chain have been found in a fairly large number of unsolved patients with non-syndromic FGD [34, 35]. *Nnt* deficient mice show disorganized adrenal gland zonation, high apoptosis, and diminished steroid production, while *NNT* knockdown in adrenal cells revealed impaired redox potential through elevated reactive oxygen species and decreased glutathione (GSH) to GSH-disulfide (GSSG) ratio [35]. Meanwhile, mutations in other genes associated with the mitochondrial redox system have been found in FGD patients including variants in *TXNRD2*, *GPX1* and *PRDX3* [34, 36].

It seems important to be aware that *NNT* is widely expressed in adrenal, heart, kidney, thyroid, and adipose tissues. Accordingly, the latest reports of older patients with PAI due to NNT mutations describe a broader phenotype with mineralocorticoid deficiency and extra-adrenal anomalies predominantly affecting the gonads (e.g., cryptorchidism, testis adenoma, precocious puberty, and azoospermia) [37]. In addition, hypothyroidism, hypertrophic cardiomyopathy and insulin-dependent diabetes mellitus have been reported [37, 38]. Phenotypical variability was seen with the same *NNT* mutations and within families informing that careful follow-up of each individual is warranted.

Several **metabolic disorders** can lead to PAI (Table 1). Most of them manifest with other characteristic anomalies. However, the X-linked form of adrenoleukodystrophy (X-ALD) due to *ABCD1* gene mutations can sometimes present first with an adrenal-only phenotype. The latest syndromic form of PAI due to a metabolic disorder is sphingosine-1-phosphate lyase (*SGPL1*) deficiency [39-41]. It manifests typically as a syndrome comprising steroid-resistant nephrotic syndrome and PAI, optionally associated with ichthyosis, primary hypothyroidism, cryptorchidism, immunodeficiency, and neurological anomalies. This novel sphingolipidosis results from impaired breakdown of sphingosine 1-phosphate (S1P). S1P regulates cell migration, differentiation, survival as well as angiogenesis and development. Identified human *SGPL1* mutations were shown to behave as recessive loss-of-function mutations affecting protein expression and localization, enzyme activity, and thus degradation of long-chain sphingoids [40]. The pathomechanism of PAI in *SGPL1* deficiency includes both compromised adrenal development as well as disrupted steroidogenesis [41]. Recent reports of patients carrying *SGPL1* mutations have broadened the clinical spectrum when finding individuals without PAI, without renal manifestations or without a central nervous phenotype [42, 43]. Long-term follow-up might be necessary to understand the whole spectrum of disease. Of 31 patients with reported *SGPL1* mutations, 27 and 26 had PAI and steroid-resistant nephrotic syndrome, respectively (80%), most of them had skin anomalies and immunodeficiency (80%), and 60% had a neurological phenotype [39-41, 44, 45].

Role of the underlying genetic diagnosis for treatment and outcome of PAI

Phenotype-genotype correlation in PAI can be difficult in both syndromic and non-syndromic forms. Generally, the clinical and biochemical phenotype of PAI and family history (including consanguinity and ancestral background) may be hinting at the underlying genetic defect. Comprehensive biochemical testing may be specifically informative for steroidogenesis disorders or metabolic diseases (e.g., X-ALD). Thus, the neonatal screening program includes testing for elevated 17-hydroxyprogesterone as a marker for 21-hydroxylase deficiency CAH (*CYP21A2*) in many countries [10]. More recently, screening for X-ALD has been recommended in the USA to allow early diagnosis for considering hematopoietic stem cell transplantation as a treatment option [46]. This screening in dried blood spots is based on the elevation of a lysophosphatidylcholine derivative C26:0-LPC of a very-long-chain fatty acid marker. However, even in these disorders a specific diagnosis at the molecular genetic level is advised to provide detailed information for personalized patient care and family counseling.

Next-generation sequencing (NGS) methods, including whole exome (WES) and genome sequencing (WGS) and hybridization techniques have revolutionized the diagnostic yield for genetic disorders over the past decade. While the gene candidate approach for defining CYP21A2 mutations is still valid in clinical routine, gene panels comprising a selected group of genes are nowadays used for the genetic work-up of PAI offering a molecular genetic diagnosis in 60-80% of cases [34, 47, 48]. For the remaining cases, TRIO WES or WGS are used to search for novel genetic defects. NGS may also reveal thus far missed genetic hits in genes known to cause PAI. For instance, predicted benign synonymous variants in the *CYP11A1* gene (Thr330= and Ser391=) were recently reported to cause PAI in 19 individuals of 13 families when occurring in a compound heterozygous state with a rare disruptive mutation [49]; corresponding mutations were then identified in a large number of European people with PAI.

Current and future therapeutic aspects and perspectives

Lack of corticosteroids will lead to life-threatening conditions in the short or long run. Treatment of all forms of PAI consists in immediate replacement of steroid hormones including glucocorticoids and mineralocorticoids as needed [1]. This can prevent affected individuals from suffering a deadly adrenal crisis. But hormonal replacement treatment is not trivial with current drugs bearing a considerable risk for adverse effects due to over- and undertreatment. Sex hormone replacement may be added, if gonadal steroidogenesis is affected. In addition, adrenal androgen excess as a consequence of negative feedback overstimulation through the HPA axis in CAH (mainly due to CYP21A2 deficiency) is often difficult to control with GC replacement only, and may therefore require additional anti-androgenic treatments, especially in females [10, 11].

Overall, there is a need for improved therapy of PAI including newer GC formulations with near-physiological, pharmacokinetic properties, and novel adrenal regenerative strategies [9-11, 50]. While

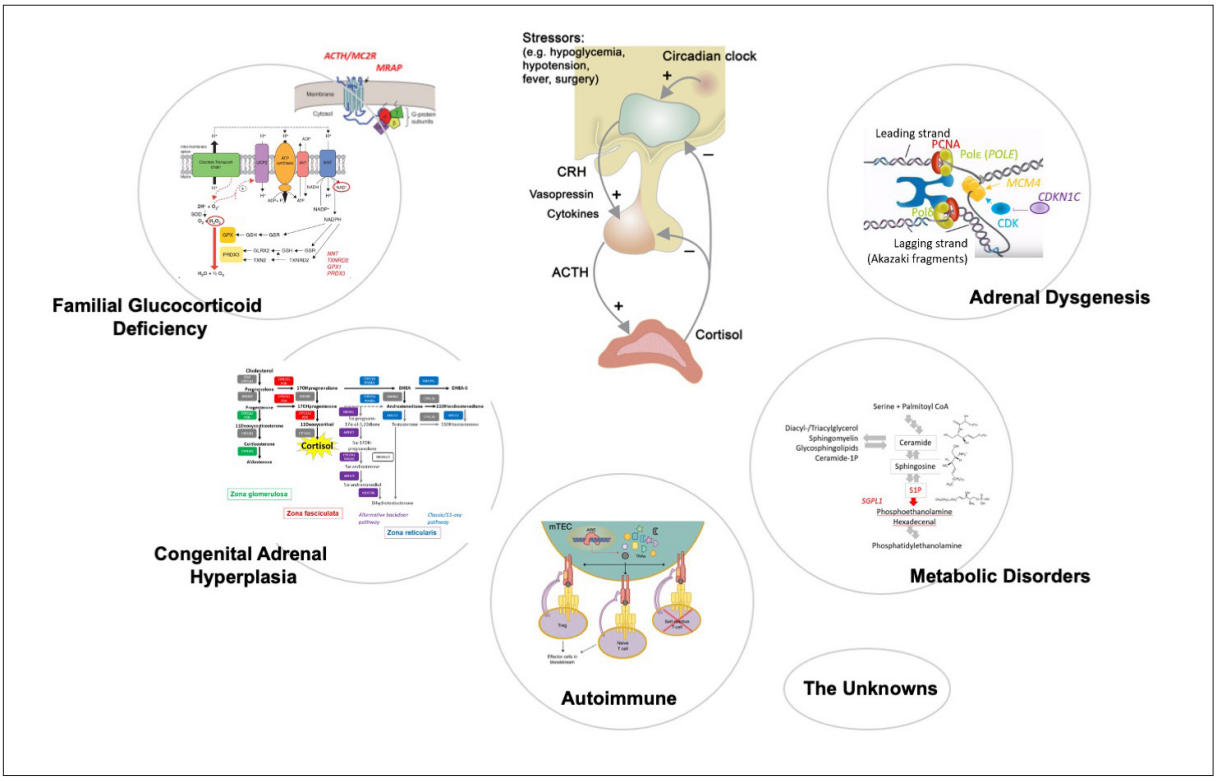

Figure 1. Schematic illustration of monogenetic causes of primary adrenal insufficiency and the regulating hypothalamic-pituitary adrenal axis. Picture assembled and redrawn from [2, 27, 53].

newer drugs and treatment modalities mimicking the circadian rhythm of physiologic cortisol production are well on their way into routine clinical care, regenerative approaches are still in the research phase. Treatment or even a cure for some monogenic forms of PAI might be feasible in the future through gene therapeutic options, but they will only become possible when the underlying genetic defect is solved. In the research setting, enzyme replacement therapy using adenoviral gene carrier vectors has been successful in transiently restoring 21-hydroxylase activity in CYP21A2 deficient mice, and may be used in humans in the near future [51]. On the other hand, permanent correction of pathogenic variants would be desirable. Gene therapy directed at patients' own stem cells could theoretically cure steroid disorders. Early studies aimed at achieving cell-based therapies have shown promising results [50], when patient-derived mesenchymal cells were reprogrammed to steroidogenic cells with functional activity [52]. The additional use of gene-editing technology may be an option for a future cure for the disease.

Conclusion

Genetic studies conducted to understand adrenal cortex development and function in health and disease are fundamental to improve diagnostic and therapeutic options for individuals with PAI, and to offer informed counseling for affected families. To date, comprehensive genetic work-up of individuals with PAI yields a diagnosis in up to 80%. This may not only have short-term consequences, but also informs on possible long-term effects that might be prevented.

Conflicts of interest

Authors declare no potential Conflicts of Interest.

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