



Review

An Update on Genetics of Adrenal Gland and Associated Disorders

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Abstract: The intricacies of human adrenal development have been under scrutiny for decades. Each year marks the identification of new genes and new interactions between gene products that ultimately will act to produce the fully functioning adult gland. Due to the complexity of this process, genetic missteps may lead to a constellation of pathologies. Recent years have identified several novel genetic causes of adrenal dysgenesis and provided new insights into previously delineated processes. *SF1*, *DAX1 (NR0B1)*, *CDKN1C*, *SAMD9*, *GLI3*, *TPIT*, *MC2R*, *MRAP*, *NNT*, *TXNRD2*, *AAAS*, and *MCM4* are among the genes which have had significant contributions to our understanding of the development and function of both adrenals and gonads. Collection and elucidation of these genetic and clinical insights are valuable tools for clinicians who diagnose and manage cases of adrenal dysfunction.

Keywords: adrenal gland; steroidogenesis; genetics; adrenal insufficiency; primary adrenal insufficiency; glucocorticoid deficiency



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1. Introduction

Human adrenal gland development is a complex process involving the orchestration of adrenal and pituitary transcription cascades with ACTH signaling pathways [1]. Due to this underlying complexity, there are many avenues via which the process of adrenal development can be disrupted. Although rare, genetic mutations are the most common cause of adrenal dysgenesis, which often presents early in infancy [2]. Abnormal adrenal gland development has also been described as part of a syndrome complex such as Meckel–Gruber syndrome, hydroletharus syndrome, pseudotriosmy 13, fetal akinesia deformation sequence (FADS), and Galloway–Mowat syndrome (Table 1). Diagnosing errors in adrenal development can be difficult due to the variety of symptoms that can manifest. Furthermore, a timely diagnosis is crucial because of the fatal outcomes many of these conditions may lead to [3]. Due in part to advances in gene sequencing technology, the list of genetic causes of adrenal dysgenesis continues to expand with each newly identified gene. These mutations can cause both primary and secondary adrenal insufficiency and present with various phenotypic symptoms depending on the specific pathogenic variant [3]. In this review, we will discuss genes that are vital for adrenal gland development, focusing on recently discovered genes and exploring insights into multiple pathogenic variants associated with adrenal gland dysgenesis/hypoplasia (Table 1).

Table 1. Summary of Genes involved in Adrenal Gland Development and Associated Conditions.

Genes	Location	Disease	Inheritance	Features	OMIM
<i>DAX1/NROB1</i>	xp21.2	X-linked adrenal hypoplasia congenita (AHC)	XLR	Hypogonadotropic hypogonadism, salt-wasting adrenal insufficiency, gonadotropin independent precocious puberty [4]	300473
<i>SF1/NR5A1</i>	9q33.3	Steroidogenic factor 1 deficiency	AD	46,XY DSD, gonadal insufficiency, hypospadias, adrenal insufficiency [5]	612965
<i>GLI3</i>	7p14.1	Pallister–Hall syndrome	AD	Adrenal hypoplasia, hypopituitarism, polydactyly, imperforate anus, hypothalamic hamartoblastoma [6]	165240
<i>WNT4</i>	1p36.12	SERKAL syndrome	AR	Female sex reversal; dysgenesis of adrenals, kidneys, lung [7]	603490
<i>TPIT</i>	1q24.2	Isolated ACTH deficiency	AR	Hypoglycemia, hypoglycemic seizures, jaundice [8]	604614
<i>AAAS</i>	12q13.13	Triple A Syndrome	AR	Adrenal insufficiency, alacrimia and achalasia cardia [9]	605378
<i>SAMD9</i>	7q21.2	MIRAGE Syndrome	AD	Myelodysplasia, infections, restricted growth, adrenal hypoplasia, gonadal anomalies and enteropathy [10]	610456
<i>MCM4</i>	8q11.21	FGD DNA Repair Defect	AR	Adrenal insufficiency, NK cell deficiency, increased chromosomal breakage and growth failure [11]	602638
<i>CDKN1C</i>	11p15.4	IMAGE Syndrome	AD; Imprinted	Intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, genital anomalies [12]	600856
<i>MC2R</i>	18p1.21	Familial Glucocorticoid Deficiency Type 1 (FGD1)	AR	Failure to thrive, hypoglycemia, jaundice, hyperpigmentation of the skin, eczema, and increased susceptibility to infection; macrocephaly, tall stature [13,14]	607397
<i>MRAP</i>	21q22.11	Familial Glucocorticoid Deficiency Type 2 (FGD2)	AR	Failure to thrive, hypoglycemia, jaundice, hyperpigmentation of the skin, eczema, and increased susceptibility to infection [13]	609196
<i>NNT</i>	5p12	FGD deficiency of mitochondrial ROS detoxification	AR	Hyperpigmentation, failure to thrive, increased susceptibility to infection in the pediatric population [15]	607878
<i>TXNRD2</i>	22q11.21	FGD deficiency of mitochondrial ROS detoxification	AR	Hyperpigmentation, failure to thrive, increased susceptibility to infection in the pediatric population [15]	606448
<i>MKS1</i>	17q22	Meckel–Gruber syndrome	AR	Cystic renal disease, CNS malformation (mostly occipital encephalocele), polydactily (mostly postaxial), and hepatic abnormalities [16]	24900
<i>WDR73</i>	15q25.2	Galloway–Mowat syndrome	AR	Microcephaly, hiatal hernia, nephrotic syndrome [17]	251300
<i>MUSK (FADS1) RAPSN (FADS2) DOK7 (FADS3)</i>	9q31.3 11p.11.2 4p.16.3	Fetal akinesia deformation sequence (FADS)	AR	Fetal akinesia, arthrogryposis, camptodactyly, facial anomalies, cardiac defects, IUGR, polyhydramnios, pulmonary and adrenal hypoplasia [18,19]	208150

Table 1. Cont.

Genes	Location	Disease	Inheritance	Features	OMIM
<i>HYLS1</i>	11q24.2	Hydrolethalus syndrome	AR	Hydrocephalus, midline defects, polydactyly, lung and heart defects [20]	236680
		Psuedotrisomy 13 syndrome	AR(?)	Holoprosencephaly, facial anomalies, polydactyly, cardiac and genital anomalies, normal chromosomes [21]	264480

OMIM: Online Mendelian Inheritance in Man; X-Linked AHC: X-Linked Adrenal Hypoplasia Congenita; XLT: X-linked recessive inheritance; AD: Autosomal dominant inheritance; AR: Autosomal recessive inheritance; DAX1: Dosage-Sensitive Sex Reversal-Adrenal Hypoplasia Critical Region on the X Chromosome, Gene 1; NR0B1: Nuclear Receptor Subfamily 0, Group B, Member 1; SF1: Steroidogenic factor 1; NR5A1: nuclear receptor subfamily 5 group A member 1; GLI3: Glioma-associated oncogene homolog 3; WNT4: Wingless-Type MMTV integration site family, member 4; TPIT: T box transcription factor. Also known as TBX19: T-Box transcription factor 19; AAAS: Aladin WD Repeat Nucleoporin; SAMD9: Sterile Alpha Motif Domain Containing 9; MCM4: Minichromosome maintenance-deficient 4; CDKN1C: Cyclin-Dependent Kinase Inhibitor 1C; MC2R: Melanocortin 2 Receptor; MRAP: Melanocortin receptor accessory protein; NNT: Nicotinamide nucleotide transhydrogenase; TXNRD2: Thioredoxin reductase 2; MKS1: MKS Transition Zone Complex Subunit 1; WDR73: WD Repeat Domain 73; MUSK: Muscle Associated Receptor Tyrosine Kinase/ GADS; RAPSN: Receptor Associated Protein Of The Synapse; DOK7: Docking Protein 7; HYLS1: HYLS1 Centriolar And Ciliogenesis Associated; MIRAGE syndrome: Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital anomalies, and Enteropathy syndrome; FGD: Familial Glucocorticoid Deficiency; IMAGE syndrome: Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital anomalies.

1.1. SF1

SF1—Steroidogenic factor 1, also referred to as *NR5A1*—is a member of the nuclear receptor superfamily located at 9q33.3. It plays an integral role in the development of the adrenal glands as well as multiple reproductive structures [22]. A variety of mutations in this gene have been identified, displaying a wide range of phenotypic presentations [9]. This is due to *NR5A1*'s broad interaction with other genes that are important in adrenal and gonadal development [23]. The mutations tend to cause errors in the DNA binding elements of the *NR5A1* [22,24]. There have been roughly 250 cases of pathology due to *NR5A1* mutations, and they tend to be heterozygous and de novo [25]. They may also be passed down by a heterozygous and asymptomatic carrier female to a male child via “sex-limited dominant” inheritance, which may falsely appear to be X-linked. Point mutations in the SF-1 A-box are implicated in 46,XX ovotesticular DSD, which may indicate that the gene is involved in sex differentiation and is here switching from ovarian to testicular development in a pathological manner [2]. Mutations in the *NR5A1* gene are classified under the umbrella term “steroidogenic factor 1 deficiency”. The clinical manifestations of *NR5A1* mutations more commonly affect the reproductive system. XY individuals often have testicular dysgenesis, severe hypospadias, and infertility. In XX individuals *NR5A1* mutations often manifest as impairment in ovarian function. It is very rare for *NR5A1* mutations to cause adrenal dysgenesis; to date, only six individuals have been reported to have SF-1 deficiency manifesting as adrenal dysfunction [2]. A recent study of 95 individuals with primary adrenal insufficiency (PAI) of unknown etiology identified one case who possessed a p.R92Q mutation in the *NR5A1* gene [26]. This individual was a 46,XX female who presented with early-onset PAI. This finding is of value because a 46,XY phenotypic female was identified in 2002 with the same homozygous change. This suggests that severe disruption of SF-1 can cause errors in adrenal development in both XX and XY individuals and should be considered once more common etiologies with similar presentations have been ruled out.

1.2. DAX1 (NR0B1)

Dosage-Sensitive Sex Reversal–Adrenal Hypoplasia Critical Region on the X Chromosome, Gene 1/Nuclear Receptor Subfamily 0, Group B, Member 1, *DAX1/NR0B1* is located on the short arm of the X chromosome (Xp21.2) and is a co-regulator of the transcription factor SF1 [27]. It is part of the nuclear receptor superfamily and regulates adrenal and

reproductive development and function [28]. Various mutations of this gene have been identified, which can cause adrenal dysgenesis. In a recent study, 12 out of 95 individuals with PAI of an unknown etiology possessed *DAX1* mutations [9]. Two specific mutations, p.W235 and p.E256, accounted for 50% of the cases identified. These mutations were due to an amino-terminal stop variant gene that results in a shortened protein or mutation of ligand-binding domain; both cause a partial loss of function [26]. In general, mutations in *DAX1/NR0B1* commonly lead to a syndrome known as X-linked adrenal hypoplasia congenita (AHC). The most common presentation of this syndrome is infertility, hypogonadotropic hypogonadism, and occasional gonadotropin-independent precocious puberty. Individuals may also present with salt-wasting adrenal insufficiency [4]. A novel missense mutation (c.884A > T, p.Leu295His) in the *DAX1* gene has been recently discovered, which resulted in a translation product with impaired ability to function as a transcriptional repressor to suppress target genes such as *STAR* [29]. This product also demonstrated impaired repression of steroidogenesis in human adrenocortical H295R cells. The presentation of this mutation was similar to AHC but also had oligospermia and testicular microlithiasis. In vitro studies confirmed reduced repressor activity, which was clinically consistent with the phenotypic presentation of the patient [30]. With the identified link of *DAX1/NR0B1* mutations to adrenal dysgenesis and patients presenting with signs of adrenal abnormalities such as late-onset AHC, genetic screening should be considered as this condition may be underdiagnosed [2].

1.3. *CDKN1C*

Cyclin-Dependent Kinase Inhibitor 1C (*CDKN1C*) was identified in 2012 in an imprinted gene cluster located on chromosome 11p15. It exerts its effects through its major role in inhibiting cell cycle progression. *CDKN1C* is also crucial for the regulation of pre- and postnatal growth and development of multiple organ systems, including the adrenal glands [31]. Under normal conditions, the paternal allele of *CDKN1C* is imprinted and the maternal allele is expressed [15]. Different mutational variants of *CDKN1C* can lead to contrasting presentations. Loss of function variants predisposes one to Beckwith–Wiedemann syndrome, whereas gain of function variants leads to the development of IMAGE syndrome [32]. Of the two syndromes caused by *CDKN1C* mutations, IMAGE syndrome is the one that presents with errors of adrenal development. The specific pathogenic variant that causes this syndrome is localized within the PCNA-binding motif of *CDKN1C*, causing impaired cell cycle S-phase progression [33]. IMAGE syndrome was first discovered in 1999 by Vilain et al. and presents with common symptoms of adrenal insufficiency [34,35]. The common phenotypic effects that define IMAGE system are Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital anomalies [36]. Apart from these symptoms, an increased chance of malignancy has been proposed. A recent case report highlighted an individual with IMAGE syndrome co-occurring with rhabdomyosarcoma [37]. Whether there is an association between mutations in *CDKN1C* and tumorigenesis, individuals with *CDKN1C* mutations should be regarded as possessing higher malignant potential.

1.4. *SAMD9*

Sterile Alpha Motif Domain Containing 9 (*SAMD9*) is another gene that, similarly to *CDKN1C*, plays a role in the development of multiple organ systems and can lead to adrenal dysgenesis when mutated [2,12]. Located on chromosome 7q21, *SAMD9* encodes a growth repressor and is thought to play a role in the recycling of growth factor receptors, utilizing endosome trafficking [38]. Heterozygous gain of function mutations predisposes affected individuals to the pathogenic presentations seen with *SAMD9*, resulting in widespread growth restriction. The majority of mutations are de novo, but some literature describes germline inheritance and variable penetrance of certain variants [12]. MIRAGE syndrome is the clinical presentation of these *SAMD9* variants and is characterized by Myelodysplasia, Infections, Restricted growth, Adrenal hypoplasia, Gonadal

anomalies, and Enteropathy [39]. Most infants with this condition are born preterm and develop salt-wasting adrenal insufficiency very early on. Novel *SAMD9* variants have resulted in the identification of new phenotypes. A recently reported de novo c.3406G>C (p. Glu1136Gln) mutation in a neonate presented with adrenal insufficiency and recurrent intussusception [5]. This report underlines the importance of a thorough approach to diagnosing MIRAGE syndrome in individuals with dysfunction in the development of multiple organ systems.

1.5. *GLI3*

Glioma-associated oncogene homolog 3 (*GLI3*) is a gene that encodes the zinc finger *GLI3* protein, a downstream target of Sonic hedgehog (SHH) signaling. SHH has been shown to play an important role in adrenal development, specifically the adrenal cortex [40]. Thus, mutations in *GLI3* that disrupt SHH signaling have been shown to cause errors in adrenal development. Pallister–Hall syndrome (PHS) is the clinical condition caused by truncation of the *GLI3* product due to frameshift mutations at 7p14.1. This connection between *GLI3* and PHS was first described in 1997 [41]. PHS follows an autosomal dominant pattern of inheritance and presents with adrenal hypoplasia, hypopituitarism, polydactyly, bifid epiglottis, imperforate anus, and hypothalamic hamartoma [42]. PHS has only been observed in a small number of individuals but may be underdiagnosed due to its variable phenotypic presentation. In 2018, a 13-year-old boy with PHS was shown to have new phenotypical characteristics not previously reported. These were identified as orofacial narrowing and a tethered spinal cord at the L3 level. Interestingly, the boy underwent spontaneous puberty and normalization of his growth pattern following treatment with growth hormone [43]. Despite the rare prevalence of this syndrome, being familiar with its presentation can aid in better future management.

1.6. *TPIT*

Disruption in the T-box transcription factor *TPIT*, also known as *TBX19*, can lead to adrenal hypoplasia in children and subsequent signs of secondary adrenal insufficiency [3]. *TPIT* regulates the production of proopiomelanocortin (POMC) in pituitary corticotrope cells through direct regulation of *POMC* gene transcription and terminal differentiation of *POMC* expressing cells [44]. Pathogenic variants in *TPIT* (1q24.2) are inherited in an autosomal recessive manner and lead to the clinical condition known as Isolated ACTH deficiency (IAD). There have been other genes involved in the development of IAD; however, multiple studies have identified *TPIT* gene mutations as the most common etiology [45]. Children with IAD present early on with symptoms of hypoglycemia, hypoglycemic seizures, and jaundice due to prolonged conjugated hyperbilirubinemia [46]. There have been various mechanisms identified that lead to loss of function of *TPIT* since its role in IAD was discovered, such as abnormal mRNA splicing or loss of *TPIT* DNA binding. A recent study also identified a neonate with IAD due to a novel homozygous synonymous mutation [29]. Although synonymous variants are commonly thought to not alter the observed protein sequence, this finding suggests that the *TPIT* gene is very sensitive to disruption and can predispose the affected individual to developing IAD.

1.7. *MC2R*

Melanocortin 2 Receptor (*MC2R*) is a gene that codes for the ACTH receptor, a G-protein coupled receptor that is crucial for ACTH signaling. Mutations in this gene have been hypothesized to cause adrenal dysgenesis through an inadequate response to ACTH stimulation from the pituitary gland [47]. This has been confirmed in rat models, where *MC2R* knockout mice had atrophied zona fasciculata within the adrenal glands. Mutations in *MC2R* (18p1.21) are inherited in an autosomal recessive manner and manifest clinically as familial glucocorticoid deficiency type 1 (FGD1) [10]. This condition presents commonly as failure to thrive, hypoglycemia, jaundice, hyperpigmentation of the skin, eczema, and increased susceptibility to infection; macrocephaly and tall stature have also

been observed [48,49]. FGD1 has a bimodal pattern of presentation and can occur later in childhood. Interestingly, individuals with FGD1 present with minor disruptions in salt homeostasis. This manifestation often leads to an incorrect diagnosis of salt-wasting adrenal hypoplasia due to it being a much more common pathology [50]. This insight should be considered when discerning between the various salt-wasting etiologies.

1.8. MRAP

The Melanocortin receptor accessory protein (*MRAP*) gene is closely related to *MC2R*, as it plays a role in facilitating ACTH signaling in the adrenal gland. The *MRAP* assists in the assembly of the ACTH receptor in the endoplasmic reticulum as well as its transport to the cell membrane [31,51]. The most prevalent *MRAP* mutations are caused by splice errors on exon 3 and are normally inherited in an autosomal recessive manner. Clinically, *MRAP* mutations cause Familial Glucocorticoid Deficiency 2 (FGD2), which is phenotypically similar to FGD1, with the age of onset occurring earlier than individuals with FGD1 [6]. Apart from *MRAP*'s role in FGD, it has also recently been shown to affect the differentiation of progenitor cells within the adrenal gland [52]. This demonstrates the direct role of *MRAP* in the embryologic development of the adrenal glands. A recent systematic analysis found that mutations in both *MC2R* and *MRAP* leading to FGD make up over one-fifth (22%) of all causes of adrenal insufficiency [48].

1.9. NNT and TXNRD2

Nicotinamide nucleotide transhydrogenase (*NNT*) was first found to play a role in adrenal development in 2012 due to its connection to FGD [53]. The form of FGD caused by *NNT* mutations is an autosomal recessive condition that presents commonly with low cortisol levels and elevated ACTH levels [54]. Phenotypic symptoms such as hyperpigmentation, failure to thrive, and increased susceptibility to infection in the pediatric population are common [53]. As previously mentioned, mutations in the *MC2R* gene are the most established cause of FGD, but comprehensive gene sequencing has more recently identified *NNT* and *TXNRD2* mutations as possible causes of FGD [53]. The *NNT* gene located on chromosome 5p12 encodes a protein located on the inner mitochondrial membrane which is responsible for pumping protons across the membrane. Mutations in this gene thus result in the disruption in oxidative stress balance and excess accumulation of ROS [8]. Analysis of a pediatric population with PAI found 10/155 (6.5%) to have mutations in *NNT*, demonstrating its prevalence among individuals with PAI symptoms [55].

Thioredoxin reductase 2 (*TXNRD2*) is another gene that operates in a similar environment to *NNT*. Located at the 22q11 locus, *TXNRD2* codes for the mitochondrial selenoprotein *TXNRD2*, which is part of the thioredoxin system. Homozygous mutations in this gene have been hypothesized to result in similar derangements of adrenal function as those found in patients with homozygous *NNT* mutations. A report of three patients with symptoms consistent with FGD found them to have stop gain mutations p.Y447X in the *TXNRD2* gene [56]. *TXNRD2* was also screened in the study mentioned above regarding *NNT*, and mutations in *TXNRD2* were identified in 4.5% of the cohort [55]. The exact mechanism through which *NNT* and *TXNRD2* cause decreased glucocorticoid activity is still unknown, but it is believed that glands that display high levels of metabolic activity, such as the adrenals, are more affected by derangements in the mitochondrial ROS detoxification [57]. Due to the established role of *NNT* and *TXNRD2* in adrenal development, individuals presenting with symptoms of FGD should be screened.

1.10. AAAS gene

The *AAAS* gene was first identified in 1996 and consequently named *AAAS* due to its role in Triple A syndrome (TAS), also known as Allgrove syndrome. This syndrome follows an autosomal recessive pattern of inheritance and presents with ACTH-resistant adrenal insufficiency, alacrimia, and achalasia cardia [13]. There are also other less specific symptoms such as deafness, mental retardation, and hyperkeratosis [31]. *AAAS* is located

on chromosome 12q13 and codes for the protein ALADIN [58]. ALADIN is expressed in all tissues to some degree but is most strongly expressed in the pituitary, adrenal gland, and pancreas [59]. ALADIN is a nucleoporin that is located on the cytoplasmic side of the nuclear pore complex [60]. The role of the ALADIN protein in the etiology of TAS is still unclear, but some reports point to the pathogenetic mechanism as impaired nuclear import of DNA repair proteins, impaired mitotic spindle formation, and an increase in oxidative stress within the cell [14,61]. This mechanism may also explain the adrenal dysgenesis observed in individuals with *AAAS* mutations. This has been confirmed by a recent study that found ALADIN downregulation led to decreased oxidative stress response and dysregulated steroidogenesis [11]. There have been 74 mutations reported in the *AAAS* gene; most are nonsense and frameshift mutations, with the remaining percentage being missense and splice-site mutations [62]. A recent case report discussed the presentation of a 19-year-old boy with the classic symptom triad of TAS. He was subsequently subjected to genetic analysis, which identified a homozygous mutation in the *AAAS* gene [63]. Another review analyzed 70 Chinese children and found that 2 children had a mutation in the *AAAS* gene, specifically c.399 + 1G > A and c.250delT. These mutations lead to a truncated ALADIN protein [30]. Although the number of reported individuals with *AAAS* mutations is exceptionally small, expanding knowledge around the variants and their phenotypic presentation will improve identification of rare syndromes.

1.11. *MCM4*

Pathogenic variants in the minichromosome maintenance-deficient 4 (*MCM4*) gene located on chromosome 8q11.21 have led to an interesting autosomal recessive condition similar to the previously described FGD [64]. *MCM4* is part of a protein complex known as *MCM2-7* helicase, which functions to synthesize DNA in the S phase [65]. Therefore, pathogenic variants in *MCM4* have been shown to cause errors in DNA repair and replication [31]. These biallelic mutations have been described as frameshifts leading to premature stops early on in the transcript, causing alterations in protein translation. The exact mechanism through which *MCM4* mutations lead to adrenal dysgenesis is unclear, but mouse models have demonstrated that *MCM* depletion results in stem cell defect [66]. The phenotypic presentation of this FGD-like syndrome is similar to the others with adrenal insufficiency as the most prevalent feature [2]. However, this condition is unique, with affected individuals suffering NK cell deficiency, increased chromosomal breakage, and growth failure [67]. This FGD-like syndrome is very rare and has only been identified in a small consanguineous population from Ireland [67]. Future screening of individuals presenting with similar symptoms of this syndrome should be considered and may lead to the identification of other populations who possess this mutation.

1.12. *WNT4*

Wingless-Type MMTV integration site family, member 4 (*WNT4*) is one of six identified genes within the *WNT* family [68]. *WNT4* is located at 1p36.12 and has been shown to play a crucial role in the development of multiple organ systems. These include the lungs, mammary gland, pituitary gland, female reproductive system, kidneys, and adrenals [69]. *WNT4* carries out these processes through a variety of pathways. One well documented mechanism is through communication with beta-catenin, a protein that can translocate to the nucleus of cells and affect the transcription of various other genes [70]. Therefore, mutations in the *WNT4* gene have the potential to cause extensive abnormalities in normal fetal development. In 2008, Mandel et al. described a novel autosomal recessive condition in three fetuses of a consanguineous family. All fetuses had similar features, including female **SEx Reversal**, **Kidney**, **Adrenal**, and **Lung** dysgenesis, leading the authors to name this condition **SERKAL** syndrome. Using a candidate gene approach, they found a novel loss of function mutation in the *WNT4* gene in all three fetuses [7]. The loss of function mutation caused substantially decreased *WNT4* mRNA levels in vivo and in vitro and downregulation of *WNT4*-dependent inhibition of beta-catenin degradation. Their

study indicates that inadequate *WNT4* gene expression can have deleterious effects on the development of various organs, including the adrenal glands.

2. Conclusions

The list of genes that play a role in adrenal gland development is extensive, due to the complexity of the gland itself. It has been suggested that there are 69 unique genes involved in adrenal gland development [71]. This number is probably underestimated and will continue to rise as more genetic profiling is performed on adrenal gland tissues. There are already many new genes that have been identified as playing a role in adrenal development and function, but this has been primarily demonstrated in mouse models. Continued investigation is likely to identify similar genes in humans. The majority of clinical conditions caused by pathogenic variants in these genes are rare and can sometimes be difficult to diagnose due to the variability in phenotypic presentation. However, treatment can significantly improve the quality of life in most individuals and often prevent death once a diagnosis is made.

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