



Overview of endocrine tumor syndromes manifesting as adrenal tumors

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Endocrine tumor syndromes constitute a group of disorders characterized by tumors in hormone-producing tissues. These conditions predominantly affect younger patients and often have a familial inheritance. Advances in molecular genetics in recent decades have facilitated the identification of several genes associated with these tumors. The recent World Health Organization classification of adrenocortical tumors integrates the latest developments in pathology, oncology, and molecular biology. In addition, this updated classification includes adrenal cortical diseases based on an understanding of germline susceptibility to these conditions and their clonal-neoplastic nature. Catecholamine-secreting tumors, including pheochromocytoma and paraganglioma, have been found to have a genetic predisposition in as many as 80% of cases. Compared to sporadic cases, endocrine tumor syndromes are more likely to present bilaterally and show synchronous or metachronous disease. This highlights the critical need for early diagnosis, intervention, and ongoing surveillance. This review focuses on the clinical manifestations and genetic basis of endocrine tumor syndromes originating from the adrenal glands.

Introduction

Endocrine tumor syndromes constitute a group of disorders characterized by tumors in hormone-producing tissue. These conditions mainly affect younger patients and often exhibit familial inheritance patterns, with sporadic cases being less common. Patients often initially present with signs and symptoms indicative of hormone overproduction. Nonetheless, non-functional tumors may become apparent due to their mass effect. Pathogenic germline mutations in tumor suppressor genes and oncogenes are implicated in the emergence of various hereditary endocrine tumor syndromes. However, pediatric cases within families may exhibit only subtle clinical signs and minor biochemical alterations, leading to potential misdiagnosis during clinical evaluations.

Over the past few decades, advances in molecular genetics have made it possible to identify many genes associated with the development of endocrine tumors in children. This has improved our understanding of the disease mechanisms, enabling an early diagnosis, timely tumor surveillance, and improved treatment strategies. This review aims to describe the clinical manifestations and molecular genetic basis of endocrine cancer syndromes, focusing on those of adrenal origin.

Ethics statement

It is a literature database-based review; therefore, neither approval by the institutional review board nor obtainment of informed consent was required.

Adrenocortical tumors

Adrenal tumors are classified into those of the adrenal cortex and those of the adrenal medulla and extra-adrenal paraganglia, according to the World Health Organization (WHO) classification of endocrine tumors [1]. Adrenocortical tumors are found in approximately 5% of the general population, with the majority being small, benign, non-functioning adrenocortical adenomas [2,3]. Adrenocortical carcinomas, however, are rare, with an incidence of 0.2 to 0.3 cases per million in adults [2,3]. Most adrenocortical tumors in adults are discovered incidentally, without excess adrenal hormone production, although 15% are functioning tumors [2]. In contrast, in the pediatric population, adrenal hormone excess is observed in about 80% to 90% of patients, with two age peaks: the first 5 years of life and adolescence [4,5]. In pediatric cases, androgen excess is the commonly observed presentation, followed by Cushing syndrome or a combination of both [4]. Therefore, it is important to consider multiple possibilities in the differential diagnosis of virilization, including androgen-secreting tumors and congenital adrenal hyperplasia [6,7]. Cushing syndrome tends to be more prevalent in older age groups [4]. Androgen excess is associated with accelerated growth, whereas cortical excess leads to a reduction in growth velocity. Therefore, clinical suspicion of adrenal tumors is warranted when patients present with symptoms of virilization and Cushing syndrome. Notably, adrenocortical carcinomas are more common in pediatric cases than in adults [8,9]. Furthermore, some cases of adrenocortical carcinomas are linked to various familial cancer syndromes, such as Beckwith-Wiedemann syndrome (BWS), Li-Fraumeni syndrome (LFS), and multiple endocrine neoplasia type 1 (MEN1) [4,10]. Untreated or inadequately treated congenital adrenal hyperplasia can also lead to the development of adrenal tumors [11,12]. Therefore, when diagnosing adrenocortical carcinoma in pediatric patients, the possibility of familial cancer syndromes must be considered. These syndromes increase the risk of other tumors and require a comprehensive management approach. Thus, a thorough differential diagnosis is essential to ensure appropriate and effective treatment strategies.

Li-Fraumeni syndrome

LFS is a hereditary cancer syndrome caused by a pathogenic mutation in the *TP53* gene. This condition is associated with a high risk of developing various childhood and adult-onset tumors, including adrenocortical carcinomas, breast cancer, soft tissue sarcomas, osteosarcomas, leukemia, and brain tumors [13,14]. The estimated lifetime cancer risk for women with LFS exceeds 90%, while it is over 70% for men [14]. Additionally, individuals with LFS face a 5% to 13% lifetime risk of developing adrenocortical carcinoma [12,15–17]. The incidence of germline *TP53* mutations is particularly high in those diagnosed with adrenocortical carcinoma during childhood, with the rate decreasing from 58% in those diagnosed before the age of 12% to 25% in those diagnosed between the ages of 12 and 20 [15]. The typical clinical presentation of LFS includes symptoms arising from glucocorticoid and androgen excess in early childhood [12]. The long-term prognosis is closely linked to the age at diagnosis and the stage of the tumor; pediatric patients with completely resected small tumors generally have a favorable prognosis

[12,18]. LFS should be considered clinically in individuals who develop a diverse range of cancers at a young age or in those with a family history of cancers such as adrenocortical tumors, breast cancer, or brain tumors. It is important to note that genetic testing for *TP53* mutations is strongly recommended for all pediatric cases of adrenocortical tumors, regardless of family history [12,19].

Beckwith-Wiedemann syndrome

BWS is a genomic imprinting disorder characterized by overgrowth and an increased risk of developing various tumors. Individuals with BWS are at a higher risk for embryonic tumors, such as Wilms' tumor, hepatoblastoma, and neuroblastoma. *IGF2* plays a significant role in the fetal development of the adrenal gland and steroidogenesis, and overexpression of *IGF2* has been observed in pediatric patients with adrenocortical tumors [20,21]. While adrenal hyperplasia and adrenal tumors can occur in BWS, they are less common than embryonic tumors. The overall tumor risk associated with BWS is approximately 5%–10%, with adrenocortical carcinoma accounting for about 7% of malignancies [22]. The incidence of adrenocortical carcinoma in patients with BWS is less than 1%. The most common adrenal masses reported in the literature are incidentally diagnosed adrenal cysts during prenatal and postnatal ultrasound screening [23]. There have also been cases of patients diagnosed with adrenal adenomas due to virilization and cortisol excess. Additionally, a few reports exist of patients with BWS and adrenocortical carcinoma presenting with Cushing's syndrome and virilization [23,24]. For patients with BWS, screening for adrenal tumors is recommended, including clinical evaluations for hormone excess, adrenal ultrasound, and monitoring serum dihydroepiandrosterone sulfate levels every 4 to 6 months [25]. However, given the relatively low incidence of adrenal tumors in BWS, there is limited data on the effectiveness of these screening methods [25].

Multiple endocrine neoplasia type 1 and 4

MEN1 is a rare hereditary cancer syndrome characterized by endocrine and extra-endocrine tumors, including parathyroid hyperplasia/adenoma, pituitary adenoma, and gastrointestinal neuroendocrine tumors. Heterozygous mutations in the *MEN1* tumor suppressor gene are identified in 80% to 90% of MEN1 cases [26]. Adrenal involvement is present in 10% of patients, and 1.4% of MEN1 cases develop adrenocortical carcinoma [27]. In approximately 6% of cases, adrenal involvement is the initial manifestation of MEN1 [27,28]. The majority of adrenocortical tumors in this condition are non-functional, although adrenocortical hormone excess is observed in 15% of MEN1 patients. Adrenocortical tumors are rare in the pediatric population [29]. While the incidence of adrenocortical tumors in LFS and BWS is likely to decrease with age, the incidence in MEN1 may increase with age. For adrenal screening in MEN1, abdominal imaging with CT or MRI is recommended every 3 years, and adrenal lesions require ongoing radiologic surveillance for signs of malignancy [30]. Biochemical evaluation is recommended for lesions larger than 1 cm or for those that present with clinical symptoms [30].

MEN4 is a newly identified MEN syndrome with phenotypic characteristics similar to MEN1. It is caused by mutations in the *CDKN1B* gene. The prevalence of *CDKN1B* mutations in patients presenting with neoplasia related to MEN1 is estimated to be approximately 2%–3% [31,32]. However, due to the limited number of reported cases and the likelihood of undiagnosed cases, the exact incidence and prevalence of MEN4 remain unclear. Additionally, there have been reports of adrenal tumors associated with MEN4, including two patients who presented with

non-functioning adrenal masses [31,32].

Bilateral macronodular and micronodular adrenal cortical disease

The understanding of germline susceptibility and the clonal-neoplastic nature of adrenocortical nodules has led to the refinement of their classification into three categories: sporadic nodular adrenocortical disease, bilateral micronodular adrenocortical disease, and bilateral macronodular adrenocortical disease (BMAD) [33]. Sporadic nodular adrenocortical disease typically presents as non-functioning and can involve one or both adrenal glands. In contrast, bilateral micronodular and macronodular adrenocortical diseases usually result in hypercortisolism and affect both adrenal glands [33]. These latter conditions are often associated with germline mutations. BMAD is characterized by adrenal nodules that are 1 cm or larger and commonly leads to Cushing syndrome, predominantly occurring in adults. The growth of adrenal nodules is related to the activation of the cAMP/protein kinase A (PKA) pathway. Activating mutations in *MC2R* and *GNAS* stimulate downstream cAMP/PKA signaling, leading to the development of BMAD [34]. Pathogenic mutations in *ARMC5*, a tumor suppressor gene, have been implicated in familial and sporadic cases of BMAD [35]. Additionally, research has revealed that BMAD is caused by a two-step genetic process in *ARMC5*: an inherited mutation, followed by a somatic second-hit mutation [35,36]. In addition, germline mutations in *MEN1*, *FH*, and *APC* have also been reported in this condition [37]. The typical age of diagnosis is usually between 40 and 60 years, and the condition is rare in children [35–37].

Micronodular adrenal cortical disease is characterized by the presence of multiple small adrenocortical nodules (<1 cm). It is subdivided into isolated micronodular adrenal cortical disease (i-MAD) and primary pigmented micronodular adrenal cortical disease (PPNAD). Carney complex is characterized by the pigmented lesions on the skin and/or mucosa, PPNAD, cardiac myxomas, and both benign and malignant endocrine tumors [38]. Irrespectively of the subtype, this disease is associated with germline mutations in *PRKAR1A* and *PRKACA* [39]. *PRKAR1A* encodes the type 1A regulatory subunit of PKA, and inactivating mutations in this gene lead to PKA dysregulation and are associated with PPNAD and other forms of adrenal cortical disease [38]. *PRKACA* encodes the catalytic isoform of PKA, and genetic defects in *PRKACA* constitutively activate PKA, resulting in cortisol-producing tumors [39]. In recent reports, mutations in *PDE11A* and *PDE8B* have been identified in patients with i-MAD [40,41]. Given the relative rarity of Cushing syndrome in children, careful consideration of the differential diagnosis, especially regarding bilateral MAD [12,42], is of paramount importance when these symptoms emerge during childhood.

Tumors of the adrenal medulla and paraganglia

Pheochromocytomas (PHEOs) are tumors that secrete catecholamines and originate from chromaffin cells in the adrenal medulla. They account for 80%–85% of all catecholamine-secreting tumors, while the remaining 10%–15% are paragangliomas (PGLs), which occur outside the adrenal glands [43]. These conditions are uncommon causes of hypertension, affecting 0.5%–2% of pediatric cases, and they typically manifest in the first decade of life [12,44–46]. Hypertension is noted in 80%–90% of affected pediatric patients and is often accompanied by symptoms such as palpitations, headaches, or sweating [12,44–46]. Historically, the "rule of 10" posited that only 10% of cases were hereditary, malignant, extra-adrenal, and bilateral. However, recent data from the European-American Pheochromocytoma-Paraganglioma Registry (EAPPR) indicate a much higher

incidence of hereditary cases among pediatric patients, with 80% of 164 pediatric patients having a germline mutation [44]. This represents a significant increase from the previously estimated 30%–40% in smaller case series [45,47,48], a change attributed to enhanced mutation screening, the identification of novel mutations, and more comprehensive population-based data from registries such as the EAPPR. These tumors are associated with hereditary cancer syndromes such as MEN2, neurofibromatosis type 1 (NF1), and von Hippel-Lindau (VHL) disease [43,49]. Germline mutations in the *SDHx* genes are frequently identified in these conditions [43]. These syndromes are inherited in an autosomal dominant pattern with variable penetrance.

Genetic testing for VHL and MEN2 is often recommended for patients diagnosed with PHEO or PGL, especially when there is an early onset or a family history of related tumors [50,51]. The presence of bilateral or multifocal PHEOs strongly suggests these hereditary syndromes. Clinical features such as retinal hemangioblastomas or clear cell renal carcinoma may point to VHL [43,50], whereas medullary thyroid cancer (MTC) or primary hyperparathyroidism might be indicative of MEN2 [52,53]. Malignant or atypical presentations are additional indications for genetic testing. This approach is essential as it informs not only the management of the current tumor but also the monitoring for other neoplasms associated with these syndromes.

Von Hippel-Lindau syndrome

VHL disease is an autosomal dominant tumor syndrome that occurs in approximately 1 in 36,000 live births [54]. It results from germline mutations in the *VHL* gene, a tumor suppressor gene that regulates blood vessel formation through the hypoxia-inducible factor [54]. Individuals with this condition are predisposed to developing highly vascularized tumors in multiple organs, including hemangioblastomas of the retina, cerebellum, and spine, renal cell carcinoma, PHEO, PGL, pancreatic cysts, and neuroendocrine tumors [54]. VHL is classified into type 1 and type 2 disease based on genotype-phenotype correlations, with PHEO associated with type 2 VHL in 25%–30% of cases [55]. PHEO in VHL typically presents in the second decade of life [54]. In children, PHEO and PGL may be the initial indicators of VHL, with cases reported in individuals as young as 5 years old [50]. VHL-associated PHEO has a high incidence of bilateral lesions in up to 60% of cases and synchronous or metachronous recurrence in 10%–30% [51]. These findings underscore the significant incidence of PHEO and PGL in patients with VHL and highlight the necessity for early and lifelong screening. In addition to abdominal imaging, annual testing of plasma metanephrines and plasma normetanephrines is recommended starting at the age of 5 [56].

Multiple endocrine neoplasia type 2

MEN2A is characterized by MTC, PHEO, and primary hyperparathyroidism, which affect 70%–80% of individuals with MEN2. The *RET* proto-oncogene plays a role in both MEN2 and sporadic or familial MTC. MTC is the most common manifestation in patients with MEN2A, presenting as early as the first 5 years of life. A smaller proportion of patients develop PHEO, with the likelihood varying based on specific *RET* mutations. Mutations in *RET* codon 634 are highly penetrant for PHEO, with the risk increasing from 25% at 30 years of age to 88% by 77 years of age [57]. PHEOs in patients with MEN2A are predominantly benign, multicentric, and bilateral [53]. Furthermore, in cases where a unilateral PHEO develops, there is a 30%–50% chance of a contralateral PHEO occurring within 10 years [58,59]. Patients with MEN2B almost invariably present with C-cell hyperplasia and MTC, and PHEO occurs in 30%–50% of cases. They also exhibit distinctive

features such as mucosal neuromas, intestinal ganglioneuromatosis, hyperflexible joints, and a Marfanoid body habitus [53]. Screening for PHEO in children is recommended to start at age 11 for those in the high and highest risk categories, and at age 16 for those in the moderate risk category. PHEO in MEN2 typically progresses, with up to 50% of cases developing bilateral lesions and 25% developing a metachronous lesion within 5–10 years [60,61]. The highly variable interval between the first and second PHEO, along with the lack of a direct correlation with the *RET* mutation, necessitates prolonged follow-up.

Neurofibromatosis type 1

NF1 is a multisystem genetic disorder that predisposes individuals to benign and malignant tumors due to mutations in the *NF1* gene [62]. This gene is responsible for producing neurofibromin, a protein that acts as a negative regulator of Ras activity [63]. When neurofibromin is lost, there is an increase in mitogenic signaling, leading to enhanced cellular proliferation or differentiation [63]. PHEOs in NF1 patients are reported in approximately 0.1%–3% of cases, with an average age of onset at 40 years; however, a prospective study has indicated a much higher prevalence of 14.6% [64,65]. The reason for this discrepancy may be the previous lack of biochemical testing, which suggests that some cases may have gone undetected. About half of the cases of PHEOs and PGLs are symptomatic [66]. Biochemical testing for these conditions, which includes measuring urine or plasma catecholamines and metanephrines, is recommended when symptoms are suggestive, during pregnancy, and before elective surgery involving general anesthesia [62]. However, routine biochemical screening for PHEOs and PGLs in adults with NF1 is not currently advised [62]. In a recent notable case, a dopamine-secreting PHEO was discovered in a 13-year-old patient with NF1 [67]. This particular tumor did not exhibit the classic symptoms of PHEO, nor were there elevated levels of metanephrines. Consequently, the physician's clinical suspicion was pivotal in the differential diagnosis of adrenal tumors, particularly in light of the patient's predisposition to cancer.

Succinate dehydrogenase-related pheochromocytomas and paragangliomas

Succinate dehydrogenase (SDH), also known as mitochondrial complex II, is a crucial enzyme for mitochondrial energy production. It is anchored to the inner mitochondrial membrane and consists of four distinct subunits: A, B, C, and D [68]. While the loss of function in *SDHB*, *SDHC*, and *SDHD* is strongly associated with the development of PHEO and PGL, data on *SDHA* are more limited [69]. Approximately 20% of patients diagnosed with PHEO or PGL carry a germline mutation in one of the *SDHx* genes [69,70]. Individuals with *SDHD* mutations exhibit high penetrance, often developing multiple tumors, predominantly in the parasympathetic region of the head and neck [68,69]. In contrast, *SDHB* mutations predispose carriers primarily to retroperitoneal PHEO and sympathetic PGL, and are associated with a more aggressive disease course, including a higher rate of malignancy and metastasis [68,69]. Data on *SDHC* mutations are scarce, but carriers typically present with non-metastatic head and neck PGLs [69]. For asymptomatic carriers of *SDHB* mutations, initial tumor screening is recommended between the ages of 6 and 10 years. For those with asymptomatic *SDHA*, *SDHC*, and *SDHD* mutations, screening should commence between the ages of 10 and 15 years [69]. In children, biochemical measurements are utilized for screening. Additionally, MRI of the head, neck, chest, abdomen, and pelvis is the recommended primary imaging modality for initial tumor screening in childhood [69].

Conclusion

Over the past 20 years, significant progress has been made in understanding the syndromes that lead to endocrine tumors, greatly improving the diagnostic and therapeutic approaches available to clinicians. These advances include the identification of key genes responsible for these tumors and the elucidation of the pathways that lead to endocrine cell hyperplasia and tumor progression. Nonetheless, challenges remain in pinpointing specific genes and determining their exact role in initiating these tumors. Alongside these genetic insights, this review has effectively outlined the incidence and clinical presentation of adrenal tumors (Table 1). This in-depth knowledge is crucial for improving patient care by facilitating early detection,

Table 1. Endocrine tumor syndromes

| Syndromes | Genes involved | Clinical manifestations | Surveillance screening |
|--|--|--|---|
| Endocrine tumor syndrome related to adrenocortical tumor | | | |
| Li-Fraumeni syndrome | <i>TP53</i> | Adrenocortical carcinoma, breast cancer, soft tissue sarcomas, osteosarcomas, leukemia, brain tumors | Abdominal ultrasound every 3 to 4 months If ultrasound is not possible, blood test every 3–4 months to measure total testosterone, dehydroepiandrosterone, and androstenedione. |
| Beckwith-Wiedemann syndrome | Abnormal methylation at 11p15.5, <i>CDKN1C</i> | Macroglossia, hemihyperplasia, omphalocele, neonatal hypoglycemia, macrosomia, embryonal tumors | Limited data on the utility of these screening methods Clinical evaluations for hormone excess |
| Multiple endocrine neoplasia type 1 | <i>RET</i> | Neoplasia of the parathyroid glands, the anterior pituitary gland, neuroendocrine tissue of gastro-entero-pancreatic organ systems | Abdominal imaging with CT or MRI is recommended every 3 years |
| Bilateral macronodular and micronodular adrenal cortical disease | <i>ARMC5</i> , <i>PRKAR1A</i> , <i>PRKACA</i> , <i>PDE11A</i> , <i>PDE8B</i> | Bilateral adrenal hyperplasia associated with one or more adrenal nodules, Cushing syndrome | |
| Endocrine tumor syndrome related to pheochromocytoma and paraganglioma | | | |
| Von Hippel-Lindau syndrome | <i>VHL</i> | Hemangioblastomas of the retina, cerebellum, and spine, renal cell carcinoma, pheochromocytoma, paraganglioma, pancreatic cysts, neuroendocrine tumors | Annual abdominal imaging and plasma metanephrine and normetanephrine testing starting at 5 years of age |
| Multiple endocrine neoplasia type 2 | <i>RET</i> | Medullary thyroid cancer, PHEO, primary hyperparathyroidism | Calcium or ionized calcium with PTH levels, plasma metanephrines and normetanephrines or 24-hour urinary metanephrines and normetanephrines starting at 11 years for those in the high and highest categories and 16 years for those in the moderate category |
| Neurofibromatosis type 1 | <i>NF1</i> | Plexiform neurofibromas, malignant peripheral nerve sheath tumors, optic pathway gliomas, breast cancer | Limited data on the utility of these screening methods |
| SDH-related disease | <i>SDHA</i> , <i>SDHB</i> , <i>SDHC</i> , <i>SDHD</i> | Early onset, multifocal disease, high rate of recurrence and metastasis | Recommended timing of initial tumor screening between the ages of 6 and 10 years in <i>SDHB</i> defects; between the ages of 10 and 15 years in <i>SDHA</i> , <i>SDHC</i> , and <i>SDHD</i> defects |

PHEO, pheochromocytoma; SDH, succinate dehydrogenase.

guiding effective management, and informing the development of targeted treatment strategies.

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Authors' contributions

The article is prepared by a single author.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary materials

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References

- Lam AK. Update on adrenal tumours in 2017 World Health Organization (WHO) of endocrine tumours. *Endocr Pathol* 2017;28(3):213-227.
- Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR. The clinically inapparent adrenal mass: update in diagnosis and management. *Endocr Rev* 2004;25(2):309-340.
- McAteer JP, Huaco JA, Gow KW. Predictors of survival in pediatric adrenocortical carcinoma: a Surveillance, Epidemiology, and End Results (SEER) program study. *J Pediatr Surg* 2013;48(5):1025-1031.
- Sandru F, Petca RC, Carsote M, Petca A, Dumitrascu MC, Ghemigian A. Adrenocortical carcinoma: pediatric aspects (review). *Exp Ther Med* 2022;23(4):287.
- Heo YJ, Yoo JH, Choe YS, Park SH, Lee SB, Kim HA, et al. Low-dose mitotane-induced neurological and endocrinological complication in a 5-year-old girl with adrenocortical carcinoma. *Ann Pediatr Endocrinol Metab* 2022;27(3):236-241.
- Markosyan R. Patients with disorders of sex development. *Ann Pediatr Endocrinol Metab* 2021;26(2):74-79.
- Lee HG, Kim CJ. Classic and backdoor pathways of androgen biosynthesis in human sexual development. *Ann Pediatr Endocrinol Metab* 2022;27(2):83-89.
- Ebbehoj A, Li D, Kaur RJ, Zhang C, Singh S, Li T, et al. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020;8(11):894-902.
- Pinto EM, Zambetti GP, Rodriguez-Galindo C. Pediatric adrenocortical tumours. *Best Pract Res Clin Endocrinol Metab* 2020;34(3):101448.
- Else T. Association of adrenocortical carcinoma with familial cancer susceptibility syndromes. *Mol Cell Endocrinol* 2012;351(1):66-70.
- Yoo HW. Diverse etiologies, diagnostic approach, and management of primary adrenal insufficiency in pediatric age. *Ann Pediatr Endocrinol Metab* 2021;26(3):149-157.
- Kim JH, Choi Y, Hwang S, Yoon JH, Kim GH, Yoo HW, et al. Clinical characteristics and long-term outcomes of adrenal tumors in children and adolescents. *Exp Clin Endocrinol Diabetes* 2023;131(10):515-522.
- Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer* 2016;122(23):3673-3681.
- Kumamoto T, Yamazaki F, Nakano Y, Tamura C, Tashiro S, Hattori H, et al. Medical guidelines for Li-Fraumeni syndrome 2019, version 1.1. *Int J Clin Oncol* 2021;26(12):2161-2178.
- Wasserman JD, Novokmet A, Eichler-Jonsson C, Ribeiro RC, Rodriguez-Galindo C, Zambetti GP, et al. Prevalence and functional consequence of TP53 mutations in pediatric adrenocortical carcinoma: a children's oncology group study. *J Clin Oncol* 2015;33(6):602-609.
- Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, et al. Germline mutations in predisposition genes in pediatric cancer. *N Engl J Med* 2015;373(24):2336-2346.
- Amadou A, Waddington Achatz MI, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. *Curr Opin Oncol* 2018;30(1):23-29.
- Michalkiewicz E, Sandrini R, Figueiredo B, Miranda ECM, Caran E, Oliveira-Filho AG, et al. Clinical and outcome characteristics of children with adrenocortical tumors: a report from the international pediatric adrenocortical tumor registry. *J Clin Oncol*

- 2004;22(5):838-845.
19. Fassnacht M, Dekkers OM, Else T, Baudin E, Berruti A, de Krijger RR, et al. European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol* 2018;179(4):G1-G46.
 20. Pinto EM, Chen X, Easton J, Finkelstein D, Liu Z, Pounds S, et al. Genomic landscape of paediatric adrenocortical tumours. *Nat Commun* 2015;6:6302.
 21. Coulter CL. Fetal adrenal development: insight gained from adrenal tumours. *Trends Endocrinol Metab* 2005;16(5):235-242.
 22. Lapunzina P. Risk of tumorigenesis in overgrowth syndromes: a comprehensive review. *Am J Med Genet C Semin Med Genet* 2005;137C(1):53-71.
 23. MacFarland SP, Mostoufi-Moab S, Zelley K, Mattei PA, States LJ, Bhatti TR, et al. Management of adrenal masses in patients with Beckwith–Wiedemann syndrome. *Pediatr Blood Cancer* 2017;64(8):e26432.
 24. Eltan M, Arslan Ates E, Cerit K, Menevse TS, Kaygusuz SB, Eker N, et al. Adrenocortical carcinoma in atypical Beckwith–Wiedemann syndrome due to loss of methylation at imprinting control region 2. *Pediatr Blood Cancer* 2020;67(1):e28042.
 25. Brioude F, Kalish JM, Mussa A, Foster AC, Blik J, Ferrero GB, et al. Clinical and molecular diagnosis, screening and management of Beckwith–Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol* 2018;14(4):229-249.
 26. Kamilaris CDC, Stratakis CA. Multiple endocrine neoplasia type 1 (MEN1): an update and the significance of early genetic and clinical diagnosis. *Front Endocrinol* 2019;10:339.
 27. Gatta-Cherifi B, Chabre O, Murat A, Niccoli P, Cardot-Bauters C, Rohmer V, et al. Adrenal involvement in MEN1. Analysis of 715 cases from the Groupe d'etude des Tumeurs Endocrines database. *Eur J Endocrinol* 2012;166(2):269-279.
 28. Kim SE, Lee NY, Cho WK, Yim J, Lee JW, Kim M, et al. Adrenocortical carcinoma and a sporadic MEN1 mutation in a 3-year-old girl: a case report. *Ann Pediatr Endocrinol Metab* 2022;27(4):315-319.
 29. Pieterman CRC, Valk GD. Update on the clinical management of multiple endocrine neoplasia type 1. *Clin Endocrinol* 2022;97(4):409-423.
 30. Newey PJ, Newell-Price J. MEN1 surveillance guidelines: time to (re)think? *J Endocr Soc* 2022;6(2):bvac001.
 31. Agarwal SK, Mateo CM, Marx SJ. Rare germline mutations in cyclin-dependent kinase inhibitor genes in multiple endocrine neoplasia type 1 and related states. *J Clin Endocrinol Metab* 2009;94(5):1826-1834.
 32. Tonelli F, Giudici F, Giusti F, Marini F, Cianferotti L, Nesi G, et al. A heterozygous frameshift mutation in exon 1 of CDKN1B gene in a patient affected by MEN4 syndrome. *Eur J Endocrinol* 2014;171(2):K7-K17.
 33. Mete O, Erickson LA, Juhlin CC, de Krijger RR, Sasano H, Volante M, et al. Overview of the 2022 WHO classification of adrenal cortical tumors. *Endocr Pathol* 2022;33(1):155-196.
 34. de Jousineau C, Sahut-Barnola I, Levy I, Saloustros E, Val P, Stratakis CA, et al. The cAMP pathway and the control of adrenocortical development and growth. *Mol Cell Endocrinol* 2012;351(1):28-36.
 35. Assié G, Libé R, Espiard S, Rizk-Rabin M, Guimier A, Luscap W, et al. ARMC5 mutations in macronodular adrenal hyperplasia with Cushing's syndrome. *N Engl J Med* 2013;369(22):2105-2114.
 36. Elbelt U, Trovato A, Kloth M, Gentz E, Finke R, Spranger J, et al. Molecular and clinical evidence for an ARMC5 tumor syndrome: concurrent inactivating germline and somatic mutations are associated with both primary macronodular adrenal hyperplasia and meningioma. *J Clin Endocrinol Metab* 2015;100(1):E119-E128.
 37. Vassiliadi DA, Tsagarakis S. Diagnosis and management of primary bilateral macronodular adrenal hyperplasia. *Endocr Relat Cancer* 2019;26(10):R567-R581.
 38. Berthon AS, Szarek E, Stratakis CA. PRKACA: the catalytic subunit of protein kinase A and adrenocortical tumors. *Front Cell Dev Biol* 2015;3:26.
 39. Lodish MB, Yuan B, Levy I, Braunstein GD, Lyssikatos C, Salpea P, et al. Germline PRKACA amplification causes variable phenotypes that may depend on the extent of the genomic defect: molecular mechanisms and clinical presentations. *Eur J Endocrinol* 2015;172(6):803-811.
 40. Horvath A, Boikos S, Giatzakis C, Robinson-White A, Groussin L, Griffin KJ, et al. A genome-wide scan identifies mutations in the gene encoding phosphodiesterase 11A4 (PDE11A) in individuals with adrenocortical hyperplasia. *Nat Genet* 2006;38(7):794-800.
 41. Horvath A, Mericq V, Stratakis CA. Mutation in PDE8B, a cyclic AMP-specific phosphodiesterase in adrenal hyperplasia. *N Engl J Med* 2008;358(7):750-752.
 42. Concepción-Zavaleta MJ, Armas CD, Quiroz-Aldave JE, García-Villasante EJ, Gariza-Solano AC, Durand-Vásquez MC, et al. Cushing disease in pediatrics: an update. *Ann Pediatr Endocrinol Metab* 2023;28(2):87-97.
 43. Bholah R, Bunchman TE. Review of pediatric pheochromocytoma and paraganglioma. *Front Pediatr* 2017;5:155.
 44. Bausch B, Wellner U, Bausch D, Schiavi F, Barontini M, Sanso G, et al. Long-term prognosis of patients with pediatric pheochromocytoma. *Endocr Relat Cancer* 2014;21(1):17-25.
 45. Park H, Kim MS, Lee J, Kim JH, Jeong BC, Lee S, et al. Clinical presentation and treatment outcomes of children and adolescents with pheochromocytoma and paraganglioma in a single center in Korea. *Front Endocrinol* 2021;11:610746.
 46. Beltsevich DG, Kuznetsov NS, Kazaryan AM, Lysenko MA. Pheochromocytoma surgery: epidemiologic peculiarities in children. *World J Surg* 2004;28(6):592-596.
 47. Pham TH, Moir C, Thompson GB, Zarroug AE, Hamner CE, Farley D, et al. Pheochromocytoma and paraganglioma in children: a review of medical and surgical management at a tertiary care center. *Pediatrics* 2006;118(3):1109-1117.
 48. Fishbein L, Merrill S, Fraker DL, Cohen DL, Nathanson KL. Inherited mutations in pheochromocytoma and paraganglioma: why all patients should be offered genetic testing. *Ann Surg Oncol* 2013;20(5):1444-1450.
 49. Lenders JWM, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SKG, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99(6):1915-1942.

50. Aufforth RD, Ramakant P, Sadowski SM, Mehta A, Trebska-McGowan K, Nilubol N, et al. Pheochromocytoma screening initiation and frequency in von Hippel-Lindau syndrome. *J Clin Endocrinol Metab* 2015;100(12):4498-4504.
51. Castro-Teles J, Sousa-Pinto B, Rebelo S, Pignatelli D. Pheochromocytomas and paragangliomas in von Hippel-Lindau disease: not a needle in a haystack. *Endocr Connect* 2021;10(11):R293-R304.
52. Dahia PLM, Clifton-Bligh R, Gimenez-Roqueplo AP, Robledo M, Jimenez C. Hereditary endocrine tumours: current state-of-the-art and research opportunities: metastatic pheochromocytomas and paragangliomas: proceedings of the MEN2019 workshop. *Endocr Relat Cancer* 2020;27(8):T41-T52.
53. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015;25(6):567-610.
54. Varshney N, Kebede AA, Owusu-Dapaah H, Lather J, Kaushik M, Bhullar JS. A review of von Hippel-Lindau syndrome. *J Kidney Cancer VHL* 2017;4(3):20-29.
55. Ong KR, Woodward ER, Killick P, Lim C, Macdonald F, Maher ER. Genotype-phenotype correlations in von Hippel-Lindau disease. *Hum Mutat* 2007;28(2):143-149.
56. Binderup MLM, Smerdel M, Borgwadt L, Beck Nielsen SS, Madsen MG, Møller HU, et al. von Hippel-Lindau disease: updated guideline for diagnosis and surveillance. *Eur J Med Genet* 2022;65(8):104538.
57. Imai T, Uchino S, Okamoto T, Suzuki S, Kosugi S, Kikumori T, et al. High penetrance of pheochromocytoma in multiple endocrine neoplasia 2 caused by germ line RET codon 634 mutation in Japanese patients. *Eur J Endocrinol* 2013;168(5):683-687.
58. Lairmore TC, Ball DW, Baylin SB, Wells SA Jr. Management of pheochromocytomas in patients with multiple endocrine neoplasia type 2 syndromes. *Ann Surg* 1993;217(6):595-601.
59. Asari R, Scheuba C, Kaczirek K, Niederle B. Estimated risk of pheochromocytoma recurrence after adrenal-sparing surgery in patients with multiple endocrine neoplasia type 2A. *Arch Surg* 2006;141(12):1199-1205.
60. Castinetti F, Waguespack SG, Machens A, Uchino S, Hasse-Lazar K, Sanso G, et al. Natural history, treatment, and long-term follow up of patients with multiple endocrine neoplasia type 2B: an international, multicentre, retrospective study. *Lancet Diabetes Endocrinol* 2019;7(3):213-220.
61. Thosani S, Ayala-Ramirez M, Palmer L, Hu MI, Rich T, Gagel RF, et al. The characterization of pheochromocytoma and its impact on overall survival in multiple endocrine neoplasia type 2. *J Clin Endocrinol Metab* 2013;98(11):E1813-E1819.
62. Carton C, Evans DG, Blanco I, Friedrich RE, Ferner RE, Farschtschi S, et al. ERN GENTURIS tumour surveillance guidelines for individuals with neurofibromatosis type 1. *eClinicalMedicine* 2023;56:101818.
63. Bergoug M, Doudeau M, Godin F, Mosrin C, Vallée B, Bénédicti H. Neurofibromin structure, functions and regulation. *Cells* 2020;9(11):2365.
64. Gruber LM, Erickson D, Babovic-Vuksanovic D, Thompson GB, Young WF Jr, Bancos I. Pheochromocytoma and paraganglioma in patients with neurofibromatosis type 1. *Clin Endocrinol* 2017;86(1):141-149.
65. Zinamosca L, Petramala L, Cotesta D, Marinelli C, Schina M, Cianci R, et al. Neurofibromatosis type 1 (NF1) and pheochromocytoma: prevalence, clinical and cardiovascular aspects. *Arch Dermatol Res* 2011;303(5):317-325.
66. Al-Sharefi A, Javaid U, Perros P, Ealing J, Truran P, Nag S, et al. Clinical presentation and outcomes of pheochromocytomas/paragangliomas in neurofibromatosis type 1. *Eur Endocrinol* 2019;15(2):95-100.
67. Lee MS, Lee R, Park SH, Kwon SH, Park JY, Lee SW, et al. Metanephrine negative pheochromocytoma: a rare case report of dopamine-secreting tumor in an adolescent neurofibromatosis type 1 patient. *Ann Pediatr Endocrinol Metab* 2022;28(4):302-307.
68. Kantorovich V, King KS, Pacak K. SDH-related pheochromocytoma and paraganglioma. *Best Pract Res Clin Endocrinol Metab* 2010;24(3):415-424.
69. Amar L, Pacak K, Steichen O, Akker SA, Aylwin SJB, Baudin E, et al. International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers. *Nat Rev Endocrinol* 2021;17(7):435-444.
70. Taschner PEM, Jansen JC, Baysal BE, Bosch A, Rosenberg EH, Bröcker-Vriends AHJT, et al. Nearly all hereditary paragangliomas in The Netherlands are caused by two founder mutations in the SDHD gene. *Genes Chromosomes Cancer* 2001;31(3):274-281.