THEMATIC REVIEW

65 YEARS OF THE DOUBLE HELIX

Endocrine tumour syndromes in children and adolescents

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Abstract

As medicine is poised to be transformed by incorporating genetic data in its daily practice, it is essential that clinicians familiarise themselves with the information that is now available from more than 50 years of genetic discoveries that continue unabated and increase by the day. Endocrinology has always stood at the forefront of what is called today 'precision medicine': genetic disorders of the pituitary and the adrenal glands were among the first to be molecularly elucidated in the 1980s. The discovery of two endocrine-related genes, *GNAS* and *RET*, both identified in the late 1980s, contributed greatly in the understanding of cancer and its progression. The use of *RET* mutation testing for the management of medullary thyroid cancer was among the first and one of most successful applications of genetics in informing clinical decisions in an individualised manner, in this case by preventing cancer or guiding the choice of tyrosine kinase inhibitors in cancer treatment. New information emerges every day in the genetics or system biology of endocrine disorders. This review goes over most of these discoveries and the known endocrine tumour syndromes. We cover key genetic developments for each disease and provide information that can be used by the clinician in daily practice.

Key Words

- ▶ endocrine tumour syndromes
- ▶ genetics
- ▶ Li-Fraumeni syndrome
- ▶ MEN1

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Introduction

In the last three decades, genetic discoveries through the advances in molecular technology have enabled the identification of many genes that have been linked with the development of paediatric malignancies including endocrine tumours, both at the germline and somatic level (Oberg *et al.* 2016, Grobner *et al.* 2018). This has led to significant progress in our understanding of the

molecular drivers and potential for novel treatment options for these neoplasms.

Benign and malignant endocrine neoplasms in childhood and adolescence form a widely heterogeneous group of disorders often presenting with subtle clinical or biochemical features that are often missed or misdiagnosed during a clinical encounter. Endocrine tumours

developing in young patients are quite characteristic for certain cancer predisposition syndromes (CPSs). A wide spectrum of non-malignant and malignant tumours within each syndrome exists, with poor genotype-to-phenotype correlation. Thus, experienced clinicians working in established centres of excellence are generally required to care for at risk or affected individuals with these syndromes.

As with many other malignancies, studies of the genomic landscape of endocrine tumours have formed the basis for understanding pathogenesis, clinical behaviour and implementing clinical trials evaluating novel targeted agents. Alterations in the *RET* gene is a classic example of an early genomic discovery directly impacting thyroid carcinoma diagnosis and management. *RET* point mutations and rearrangements in thyroid carcinoma have led to a wider therapeutic arsenal with tyrosine kinase inhibition. At a germline level, *RET* genotype-phenotype correlations have been established in patients with multiple endocrine neoplasia type 2 (MEN2), which impacts our tumour surveillance and prevention strategies. The identification of links between CPS and endocrine neoplasms has also contributed to our knowledge of tumour molecular drivers. The implication of Wnt pathway signalling in papillary thyroid carcinoma (PTC) and its cribriform-morular variant was recognised through the association in patients with familial adenomatous polyposis and thyroid carcinoma.

These examples illustrate only a few of the impacts of genetics in childhood endocrine tumours in this era of molecular genomics. This review focuses on the established and novel germline and somatic features of endocrine tumours in childhood and adolescence, highlighting the influence of genomics in our current understanding of their pathogenesis and clinical behaviour. Each section

included in this review is subdivided in the same manner, starting with the neoplasm classification and molecular features, followed by a description of the associated CPS. CPSs are featured in the section where the association is the highest with the tumour type. A timeline featuring the first descriptions of these endocrine tumour-related CPSs and their genetic background is shown in Fig. 1.

Adrenal tumours

Classification and molecular features

An adrenal tumour or mass represents an overgrowth of adrenal tissues that arises from within the adrenal cortex or medulla. These tumours can be unilateral or bilateral with a tendency to overproduce hormones. They are broadly classified as adrenocortical adenomas (ACAs), adrenocortical hyperplasia, pheochromocytomas and adrenocortical cancer (ACC) (Stratakis & Boikos 2007). A careful histologic examination of the adrenal tissue by an experienced pathologist is a critical step in subtyping the various types of adrenal tumours. In a postmortem study of patients over 50 years of age, adrenocortical hyperplasia and ACAs were present in 36% and 5% of cases, respectively (Saeger *et al.* 1998). Conversely, these lesions are extremely rare in childhood and adolescence. Their presence should raise the possibility of an inherited condition. Moreover, ACCs are rare with an incidence of 0.5–2 million per year, affecting females across all ages with higher frequency (ratio of female to male ranges from 1.5 to 2.5:1) and a median age of diagnosis of ~46 years. In childhood, ACCs represent as many as 1.3% of all cancers in children (Icard *et al.* 2001), with a worldwide incidence of ~0.3 million per year and higher figures in Southern Brazil (3.4–4.2 million per year) (Custodio *et al.* 2012).

Figure 1

This timeline represents, to the best of our knowledge, the year of the first description of the cancer predisposition syndrome, the year of the discovery of the genes that are implicated with these diseases and the year where the association was made between each gene and disease. In red, year of the first description of the disease; in blue, year of gene discovery; in purple, year in which the association was made between the gene and the disease. BWS, Beckwith–Wiedemann syndrome; CC, Carney complex; *DICER1*, *DICER1* syndrome; FAP, familial adenomatous polyposis; LFS, Li–Fraumeni syndrome; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; HPPS, hereditary pheochromocytoma and paraganglioma syndrome; HPT-JT, hyperparathyroidism–jaw–tumour syndrome; MEN1, multiple endocrine neoplasia type 1; MEN2, multiple endocrine neoplasia type 2; NF1, neurofibromatosis type 1; PHTS, PTEN hamartoma tumour syndrome; MEN4, multiple endocrine neoplasia type 4; vHL, von Hippel–Lindau.

The advances in genetic technologies and testing have enabled the subclassification of these tumours. This is particularly important for those presenting as hyperplasia or ACC; culprit pathogenic germline variants will help identify the syndrome in question, which in turn affects management and family counselling and testing.

Adrenocortical adenoma

Approximately 10% of ACAs are functional and are subdivided into aldosterone-, cortisol- and/or androgen-producing adenomas. ACAs are small (typically less than 5 cm), well-circumscribed, solid lesions that appear as bright yellow due to their enriched cytoplasmic lipid. Approximately, 75–90% of adrenocortical tumours leading to Cushing syndrome are caused by unilateral cortisol-producing adenomas, half of them bearing a somatic mutation in the *PRKACA* gene (Lodish & Stratakis 2016).

Adrenocortical hyperplasia

Adrenocortical hyperplasia are divided into two broad categories – micronodular (<1 cm in diameter) or macronodular (>1 cm in diameter) (Stratakis & Boikos 2007). Secondary bilateral adrenocortical hyperplasia with or without autonomous functioning can be observed with ACTH stimulation from either ectopic ACTH secretion or Cushing disease (Stratakis & Boikos 2007). In micronodular hyperplasia, the presence of pigmentation (i.e. mainly lipofuscin) within the lesion or the surrounding adrenal cortex is characteristic of primary pigmented nodular adrenocortical disease (PPNAD). PPNAD is usually diagnosed in children and young adults, and is either pigmented, as seen in Carney complex (CNC), or isolated (iPPNAD). Isolated micronodular adrenocortical hyperplasia (iMAD) is the other major subtype of micronodular hyperplasia and usually presents in infancy with severe Cushing syndrome. iMAD is histologically characterised by moderate diffuse cortical hyperplasia with multiple small yellow-to-dark brown nodules surrounded by a cortex with a uniform appearance. Mutations in *PRKAR1A*, *PDE11A*, *PDE8B* or germline duplications of *PRKACA* have been implicated in iMAD. Two important phosphodiesterases, which represent enzymes that hydrolyse cyclic AMP (Francis *et al.* 2011, Azevedo *et al.* 2014), have been implicated in micronodular adrenocortical diseases: *PDE8B* and *PDE11A*. Genetic polymorphisms in these genes may be low-penetrance alleles that predispose to adrenocortical tumours. *PDE8* encodes two highly specific enzymes (PDE8A and PDE8B) responsible for degrading cyclic AMP

(Lakics *et al.* 2010). The first report of mutations in *PDE8B* in iMAD was described in a 2-year-old girl who harboured a novel germline missense mutation in *PDE8B* (c.914A>C, p.P305H) that she inherited from her father (Horvath *et al.* 2008). This example highlights the progress in molecular diagnostic technology allowing genetic discoveries in rare adrenocortical tumours.

Macronodular hyperplasia is usually diagnosed in adults >50 years and can be either sporadic or familial. The most common cause of macronodular hyperplasia is primary bilateral macronodular adrenocortical hyperplasia (PBMAH), which represents a heterogeneous benign disorder responsible for ~10% and 15% of Cushing syndrome in young adulthood and childhood, respectively (Stratakis & Boikos 2007). Various biochemical patterns may be observed, including overt Cushing syndrome, co-secretion of aldosterone and cortisol (or its precursor steroids, and even oestrogens) or aldosterone only (Bourdeau *et al.* 2007, Hsiao *et al.* 2009). Cortisol secretion may be mediated by non-mutated aberrant receptors of gastrointestinal peptide, vasopressin, serotonin, catecholamines, luteinising hormone or autocrine/paracrine ACTH, among other factors (Bourdeau *et al.* 2001, Lacroix *et al.* 2010). Pathogenic variants in the tumour suppressor *ARMC5* were identified >50% of apparent sporadic and familial PBMAH cases, where both alleles carried one germline and one somatic mutation each (Assie *et al.* 2013, Alencar *et al.* 2014, Faucz *et al.* 2014). A second somatic defect, either 16p loss of heterozygosity or a second somatic mutation in the coding region of *ARMC5* is required in addition to the germline mutation in *ARMC5* to mediate tumourigenesis leading to polyclonal nodularity (Correa *et al.* 2015). Genetic variance is observed in *ARMC5*, where the second new ('private') and completely inactivating somatic *ARMC5* defect is present in each respective nodule in addition to the germline variant (Correa *et al.* 2015). PBMAH due to *ARMC5* mutations tends to have larger adrenal glands, with increased frequency of nodules and severe hypercortisolaemia (Espiard *et al.* 2015). Other genetic defects leading to PBMAH include activating mutations of *GNAS* without features of McCune-Albright syndrome (Fragoso *et al.* 2003, Hsiao *et al.* 2009), germline pathogenic variants in *PDE11A*, *FH*, *MEN1* and *APC* (Fragoso *et al.* 2003, Hsiao *et al.* 2009). Germline duplications of *PRKACA* resulting in copy number gains have been reported in one family that presented with PBMAH (Beuschlein *et al.* 2014). Predictive testing of at-risk children and adolescents in a family with PBMAH is an important aspect of genetic testing and counselling.

From our experience (NICHD, NIH), children harbouring a damaging pathogenic mutation in *AMRC5* do not develop adrenocortical hyperplasia in early childhood.

Familial syndromes

Li-Fraumeni syndrome

Li-Fraumeni syndrome (LFS) is an autosomal dominant condition due to pathogenic variants in *TP53* that predisposes to multiple cancer types (Table 1). The lifetime risk of cancer development is 75% in men and 93% in women, with approximately half of patients symptomatic by age 30 years (Sorrell *et al.* 2013, Testa *et al.* 2013). Highly penetrant disease with early-onset cancers is seen with mutations in the DNA-binding portion of *TP53*. ACC in childhood is a characteristic feature of LFS and is 2.7-fold more common in girls (Amadou *et al.* 2018). While 50–80% of these tumours in children are due to germline *TP53* pathogenic variants, only ~10% of all LFS patients develop ACC at a median age of 3 years (Rodriguez-Galindo *et al.* 2005, Gonzalez *et al.* 2009, Amadou *et al.* 2018). When compared to somatic *TP53*-mutant ACCs, their germline counterparts are larger, more aggressive, with greater resistance to chemotherapy/radiation and overall rates of relapse (Sorrell *et al.* 2013). In Southern Brazil, the prevalence of children with adrenocortical tumours is ~15-fold higher than in the rest of the world and related to a founder germline *TP53* mutation (p.R337H) (Ribeiro *et al.* 2001, Pinto *et al.* 2004). The prevalence of this mutation reaches 0.3% with a penetrance of ~2% for adrenocortical tumours; newborn screening strategies for the detection of this founder mutation in Southern Brazil have been shown to be advantageous (Custodio *et al.* 2013). ACCs in childhood should warrant testing for LFS. Along with choroid plexus carcinoma, rhabdomyosarcoma and medulloblastoma, ACCs account for the predominant cancer types seen in children with LFS.

Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome (BWS) is the prototypical disorder of genetic imprinting with an estimated prevalence of ~1/10,000 (Mussa *et al.* 2013). Children with BWS are predisposed to developing adrenocortical hyperplasia and lesions, such as adenomas, cysts and ACC (in approximately 1% of affected children) (Else 2012). Conversely, adults with BWS do not seem to have an increased risk of tumour development. ACC is also seen in idiopathic lateralised overgrowth, which shares features with BWS (Tan & Amor 2006). BWS affects females and

males equally and is caused by alterations in two domains that regulate methylation and maintain a normal balance between maternally expressed growth suppressors and paternally expressed growth promoters. These include regions centre 1 (IC1), which regulates the expression of *IGF2* and *H19* in domain 1, and imprinting centre 2 (IC2), which regulates the expression of *CDKN1C*, *KCNQ10T1* and *KCNQ1* in domain 2 (Shuman *et al.* 1993). The clinical features of BWS are presented in Table 1. Recently, a comprehensive consensus statement including a scoring system for genetic testing in patients with clinical features of BWS was presented by Brioude *et al.* (2018).

Carney complex

The main neuroendocrine manifestation of CNC is Cushing syndrome from PPAD, which is biochemically diagnosed in approximately 60% of patients. PPAD presents with mild and progressive hypercortisolaemia that is often treated with bilateral adrenalectomy. The prevalence of CNC is unknown, but over 800 cases are known (Stratakis, unpublished data), with a mean age of diagnosis of 20 years. CNC is a rare autosomal dominant hereditary multiple neoplasia syndrome that predisposes to the formation of pigmented skin lesions (lentiginosis and blue nevi) and various endocrine neoplasms including pituitary somatotroph and thyroid tumours (Table 1).

Three distinct loci of CNC exist without a clear phenotypic difference. CNC type 1 (CNC1) is caused by mutations in *PRKAR1A*, an apparent tumour suppressor gene, which encodes for the R1a subunit of PKA with an overall penetrance of >95% by the age of 50 years (Stratakis *et al.* 2001). More than 60% of patients with CNC carry germline-inactivating mutations in R1a that are spread along the whole coding sequence, with the majority leading to a premature stop codon by nonsense or frame shift (Kirschner *et al.* 2000, Horvath *et al.* 2010). A more severe phenotype is observed with in-frame deletion of exon 3 and the c.708+1G>T mutation of *PRKAR1A* (Groussin *et al.* 2006). The hot spot c.491-492delTG mutation is most closely associated with lentigines, cardiac myxoma and thyroid tumours when opposed to all other *PRKAR1A* mutations. Approximately 50% of pathogenic mutations in *PRKAR1A* (c.709(-7)del6 or c.1A>G/p.M1V) present with a mild subtype of CNC that is diagnosed before 8 years of age and manifest with seemingly iPPAD, with or without lentigines. The second locus, CNC type 2 (CNC2), is due to alterations in a yet-unidentified gene on chromosome 2p16, which occurs later in life with a lower frequency of myxomas, schwannomas, thyroid tumours

Table 1 Endocrine tumour predisposition syndromes.

Syndrome (inheritance)	Gene	Chr. locus	Endocrine features	Non-endocrine features presenting in children and adolescents	OMIM
Beckwith-Wiedemann syndrome (variable)	<i>CDKN1C</i> , other	11p15.4	ACC Cytomegaly of the fetal adrenal cortex Hyperinsulinism	Wilms tumour, hepatoblastoma, lateralised overgrowth, macrosomia, macroglossia, omphalocele/umbilical hernia, neonatal hypoglycaemia	130650
Carney complex (AD)	<i>PRKAR1A</i> , other	17q24.2	PPNAD Thyroid carcinoma Pituitary adenoma ^{*,#,%}	Skin pigmentary anomalies (lentigines), myxoma of the heart, breast and skin, large calcifying Sertoli cell tumours of the testis, psammomatous melanotic schwannomas	160980
Carney-Stratakis syndrome (AD)	<i>SDHA</i> <i>SDHB</i> <i>SDHC</i> <i>SDHD</i>	15p15.33 1p36.13 1q23.3 11q23.1	PPGL/ACT/PBMAH PPGL/ACT/PBMAH PPGL/ACT/PBMAH PPGL/ACT/PBMAH	GIST	606864
Carney triad	<i>SDHC</i> promoter methyl ^a	1q23.3	PPGL ACA PBMAH	GIST, pulmonary chondroma, oesophageal leiomyoma, sarcoma	604287
DICER1 syndrome (AD)	<i>DICER1</i>	14q32.13	MNG DTC PitB	PPB, oSLCT ^e , cystic nephroma, eRMS of the cervix, CBME, Pineoblastoma	601200
Familial adenomatous polyposis (AD)	<i>APC</i>	5q22.2	NMTC ^c	GI adenomas, colorectal cancer, desmoid tumours, Gardner fibroma, hepatoblastoma, medulloblastoma, odontomas, osteomas	175100
Familial isolated pituitary adenoma (AD)	<i>AIP</i>	11q13.2	Pituitary adenoma ^{*,#,%,&!}	–	102200
Familial PPGL (AD)	<i>SDHA</i> <i>SDHB</i> <i>SDHC</i> <i>SDHD</i> <i>SDHAF2</i> <i>FH</i>	5p15.33 1p36.13 1q23.3 11q23.1 11q12.2 1q43	PPGL PBMAH ACT PPGL	RCC	A: 614165 B: 185470 C: 602413 D: 602690 AF2: 601650
Hereditary leiomyomatosis renal cell carcinoma (AD)				RCC (papillary type II), cutaneous and uterine leiomyomatosis	150800
HyperPTH-jaw tumour syndrome/familial isolated hyperPTH (AD)	<i>CDC73</i>	1q31.2	pHPT Parathyroid carcinoma	Ossifying fibroma of the jaw, renal cysts and tumours	145001 145000
Li-Fraumeni syndrome (AD)	<i>TP53</i>	17p13.1	ACC	Hypodiploid ALL, pre-menopausal breast cancer, CPC, brain tumours, bone and soft-tissue sarcomas	151623
McCune-Albright syndrome	<i>GNAS</i>	20q13.32	Gonadotropin independent precocious puberty Leydig and/or Sertoli cell hyperplasia (testis) Growth hormone excess Neonatal hypercortisolism Pituitary adenoma ^{*,#}	Polyostotic fibrous dysplasia, CALs	174800

(Continued)

Table 1 Continued.

Syndrome (inheritance)	Gene	Chr. locus	Endocrine features	Non-endocrine features presenting in children and adolescents	OMIM
Multiple endocrine neoplasia type 1 (AD)	<i>MEN1</i>	11q13.1	GEP NETs (typically pancreatic) pHPT/parathyroid tumours ACT Pituitary adenoma ^{*,#,%,&!}	Multiple facial angiofibromas, collagenomas, lipomas	131100
Multiple endocrine neoplasia type 2a/familial medullary thyroid carcinoma (AD)	<i>RET</i>	10q11.21	MTC Parathyroid adenoma/ pHPT PPGL Pituitary adenoma [%]	Cutaneous lichen amyloidosis	171400 155240
Multiple endocrine neoplasia type 2b (AD)	<i>RET</i>	10q11.21	MTC, C-cell hyperplasia Pituitary adenoma [%]	Lip/tongue/eyelid mucosal neuromas, medullated corneal nerve fibres, marfanoid habitus, ganglioneuromatosis of the GI tract	162300
Multiple endocrine neoplasia type 4 (AD)	<i>CDKN1B</i> , other	12p13.1	Parathyroid tumours/ pHPT ACT ^d NET ^d Pituitary adenoma ^{*,%,&!} Differentiated thyroid carcinoma ^{b,d}	Tumours of the kidney, ovary, meninges ^d	610755
Neurofibromatosis type 1 (AD)	<i>NF1</i>	17q11.2	PPGL	CALs, axillary/inguinal freckling, neurofibroma, MPNST, lisch nodules, OPG, learning disabilities	162200
PTEN hamartoma tumour syndrome (AD)	<i>PTEN</i>	10q23.31	Nodular thyroid hyperplasia Thyroid carcinoma	Macrocephaly, autism/developmental delay, skin features (oral papillomas, trichilemmomas, lipomas, penile freckling), GI polyps, arteriovenous malformations, hemangioma	601728
von Hippel-Lindau (AD)	<i>VHL</i>	3p25.3	Pancreatic NETs PPGL	Renal cysts, RCC (clear cell), hemangioblastoma (retina/CNS) endolymphatic sac tumours, pancreatic cysts, cystadenomas of the epididymis and broad ligament	193300
X-linked acrogigantism (sporadic > AD)	<i>GPR101</i>	Xq26.3	Pituitary adenoma ^{*,#}	None	300942

^aRecently described in some cases; ^brarely reported; ^ccribriform-morular variant is suggestive of familial adenomatous polyposis; ^ddescribed in adults;

^ecan include endocrine manifestations; ^{*}somatotropinoma; [#]somatotrophinoma; [%]corticotropinoma; [!]prolactinoma; [&]non-functional adenoma.

ACA, adrenocortical adenoma; ACC, adrenocortical carcinoma; ACT, adrenocortical tumour; ALL, acute lymphoblastic leukaemia; CALs, café-au-lait spots; CBME, ciliary body medulloepithelioma; CPC, choroid plexus carcinoma; GEP NETs, gastro-entero-pancreatic neuroendocrine tumours; GI, gastrointestinal; GIST, gastrointestinal stromal tumour; DTC, differentiated thyroid carcinoma; eRMS, embryonal rhabdomyosarcoma; MNG, multinodular goitre; MPNST, malignant peripheral nerve sheath tumour; MTC, medullary thyroid carcinoma; NMTC, non-medullary thyroid carcinoma; oSLCT, ovarian Sertoli-Leydig cell tumour; OPG, optic pathway glioma; PBMAH, primary bilateral macronodular adrenocortical hyperplasia; pHPT, primary hyperparathyroidism; PitB, pituitary blastoma; PPB, pleuropulmonary blastoma; PPNAD, primary pigmented nodular adrenocortical disease; PPGL, pheochromocytoma and paraganglioma; PTEN, phosphatase and tensin homologue; RCC, renal cell carcinoma.

and LCCSCT. CNC type 3 (CNC3) is due to *PRKACB* or *PRKACA* amplification. Inactivating mutations in the highly polymorphic *PDE11A* were also reported in patients with PPNAD, likely representing modifier genes

(Libe *et al.* 2011). CNC predisposes to the development of benign and malignant thyroid disease, typically in a multifocal pattern (Carney *et al.* 2018). The incidence of DTC, both PTC and FTC, is between 2.5 and 5% in patients

with CNC, and thyroid tumours have been reported in patients as young as 13 years (Radin & Kempf 1995). With the advent of neck ultrasound surveillance protocols, 60–75% of patients are found to have thyroid pathology, most commonly multiple adenomatous nodules and follicular adenoma (Stratakis *et al.* 1997, Dotto & Nose 2008). Paediatric patients with CNC may also present with failure to thrive (Tirosh *et al.* 2018). The diagnosis of CNC is established if two or more of major manifestations exist (Stratakis *et al.* 1993).

Hereditary leiomyomatosis and renal cell cancer

While the predominant clinical manifestations of hereditary leiomyomatosis and renal cell cancer (HLRCC) are cutaneous and uterine leiomyomas and renal cell carcinoma, it is estimated that 8% of patients with HLRCC develop adrenocortical lesions, including PBMAH, or isolated non-functional adrenal nodularity (Matyakhina *et al.* 2005). A handful of cases of pheochromocytoma, paraganglioma as well as one case describing an ACC have been described in patients with HLRCC in the recent literature (Clark *et al.* 2014, Guo *et al.* 2017). HLRCC is an autosomal dominant disorder caused by a pathogenic germline variant in the tumour suppressor gene fumarate hydratase (*FH*). Alterations in *FH* cause activation of the hypoxia-induced factor 1 pathway that lead to tumourigenesis through enhanced glycolytic activity, neovascularisation and downregulation of apoptotic mechanisms. Clinical diagnostic criteria were proposed by Smit *et al.* (2011) and include the features described in Table 1.

Carney-Stratakis syndrome

Carney-Stratakis syndrome (CSS) is a rare autosomal dominant syndrome due to germline pathogenic variants in *SDHA*, *SDHB*, *SDHC* or *SDHD* (collectively referred to as SDHx) that predisposes to gastrointestinal tumours (GISTs), paragangliomas and adrenocortical tumours (Carney & Stratakis 2002). These mutations result in destabilisation of the mitochondrial complex and impaired SDH protein expression. *SDHD/KIT* double-mutated GISTs have also been reported. CSS should be suspected in an individual with early-onset paraganglioma or GISTs (particularly if they co-exist). The diagnosis of CSS is made by clinical, radiologic and immunohistochemical analysis. GISTs that are *KIT*- and *PDGFRA* mutation negative should raise suspicion for CSS. Absence of SDHB tumour staining in CSS tumours, an indicator of complex II disruption, is

a reliable marker for the diagnosis of CSS in the right clinical setting (Gaal *et al.* 2011).

Carney triad

Carney triad (CT) is a rare sporadic condition that predisposes to hamartomatous lesions in various organs (Table 1), with the classic triad of pulmonary chondroma, GIST and PPGL. CT is one of the few conditions that has among its clinical manifestations adrenocortical and medullary involvement, such as coexisting PBMAH or ACA and pheochromocytomas (Carney *et al.* 1977). In one study of 63 patients, 9.5% harboured variants in the *SDHA*, *SDHB*, *SDHC* and *SDHD* or loss of regions on the short arm (1p) and the long arm (1q) of chromosome 1 (Boikos *et al.* 2016). A recurrent aberrant DNA methylation at the gene locus of *SDHC* has been described in association with CT (Haller *et al.* 2014); this is understood to be the molecular signature of CT and serves today as diagnostic for the disease. Activating mutations in *KIT*- or *PDGFRA* are not generally observed in CT (Matyakhina *et al.* 2007), although in a few case reports, somatic *KIT* mutations have been seen in CT-associated GISTs.

Familial hyperaldosteronism

Familial hyperaldosteronism represents a rare group of autosomal dominant disorders that are estimated to affect <2% of patients with primary aldosteronism. Familial hyperaldosteronism type 1 (FH-I), previously known as glucocorticoid-remediable aldosteronism (GRA), is an autosomal dominant condition that is characterised by severe early-onset primary aldosteronism (<20 years old) due to a chimeric fusion of *CYP11B2* and *CYP11B1*. This genetic alteration renders the aldosterone synthase hybrid gene to be under the regulation of ACTH rather than the renin-angiotensin system (Lifton *et al.* 1992), leading to increased production of aldosterone and hybrid steroids, such as 18-oxocortisol and 18-hydroxycortisol. Significant phenotypic and biochemical heterogeneity exist, in that some individuals may never develop hypertension. Adrenocortical tumours have been reported in association with FH-I (Jeunemaitre *et al.* 1995). A family history of primary aldosteronism with or without early cerebral haemorrhage (<40 years) from intracranial aneurysms or haemorrhagic strokes should raise the suspicion for FH-I.

Familial hyperaldosteronism type 2 (FH-II) is the most common form of the disease that arises due to alterations in a yet-unidentified gene on chromosome 7p22 and characterised by adult-onset hyperaldosteronism from adrenocortical hyperplasia, aldosterone-producing

adenoma or both (Torpy *et al.* 1998, Lafferty *et al.* 2000). Recently, a multiplex family with FH-II had 8 probands with novel heterozygous variants in *CLCN2*, which encodes a voltage-gated chloride channel expressed in adrenal glomerulosa (Scholl *et al.* 2018). Familial hyperaldosteronism type 3 (FH-III) is caused by germline heterozygous mutations in *KCNJ5*, encoding the potassium channel Kir3.4, which presents in childhood or young adults with severe hypertension and metabolic derangements due to adrenocortical hyperplasia (Geller *et al.* 2008, Monticone *et al.* 2017). Familial hyperaldosteronism type 4 (FH-IV) has been recently described due to germline gain-of-function mutations in *CACNA1H* and characterised by early-onset primary aldosteronism from adrenocortical hyperplasia and seizures (Scholl *et al.* 2015).

Other familial pheochromocytoma and paraganglioma syndromes

Familial pheochromocytoma and paraganglioma (PPGL) syndromes are characterised by pheochromocytomas and paragangliomas due to germline pathogenic variants in four nuclear genes that encode the four subunits of the mitochondrial enzyme succinate dehydrogenase (SDH), collectively referred to as *SDHx*. These genes include *SDHA* (PGL5), *SDHB* (PGL4), *SDHC* (PGL3) and *SDHD* (PGL1). Alterations in *SDHAF2* (PGL2) leads to a dysfunctional protein required for flavination of SDHA (Hao *et al.* 2009). When compared to adults, paediatric patients with PPGLs carry a higher prevalence of hereditary, extra-adrenal and metastatic PPGLs (Pamporaki *et al.* 2017). Additionally, most paediatric patients with metastatic PPGL had primary extra-adrenal tumours and harboured *SDHB* (PGL4) mutations (King *et al.* 2011).

Neurofibromatosis type 1

Neurofibromatosis type 1 (NF1) is an autosomal dominant syndrome that affects 1/3000 individuals and caused by inactivating mutations in the *NF1* gene (Evans *et al.* 2010). Approximately half of cases result from *de novo* mutation in *NF1* (Evans *et al.* 2010). The *NF1* gene encodes neurofibromin, which is normally involved in the downregulation of the RAS/MAPK signalling pathway. *NF1*-inactivating mutations result in the constitutive upregulation of RAS, an important oncogene located upstream of mTOR (Martin *et al.* 1990). Only 6% of patients with NF1 develop PPGLs (Walther *et al.* 1999a), likely representing an underestimate of the prevalence in this population (Fishbein & Nathanson 2012). PPGLs typically

develop from the 4th decade onwards, are unilateral, and localised to the adrenal glands in ~90% of cases (Bausch *et al.* 2006). NF1 was identified in 4% of adolescent cases of pheochromocytomas (age range 14–17 years); these tumours had a tendency for higher malignancy potential (Bausch *et al.* 2014, Giovannoni *et al.* 2014). A poor genotype–phenotype correlation exist between *NF1* mutations and PPGL development (Tonsgard *et al.* 1997). Other manifestations of NF1 are featured in Table 1.

von Hippel-Lindau

The von Hippel-Lindau (VHL) tumour spectrum classically includes retinal, cerebellar and spinal hemangioblastomas, endolymphatic sac tumours, clear cell renal cell carcinoma (ccRCC), PPGL, pancreatic and renal cysts, non-functional pNET and epididymal and broad ligament cystadenoma. These tumours could be challenging to treat as they may present in surgically unresectable areas that rapidly grow and cause mass effects. CNS hemangioblastoma followed by ccRCC are the leading causes of mortality in patients with VHL.

Genotype–phenotype correlations have been clearly defined in VHL and are stratified into two main disease subtypes clinically differing according to the risk of PPGL development. VHL type 1 and 2 are then subcategorised according to risk of ccRCC and CNS disease. VHL type 1a and b are associated with truncating mutations or exon deletions, and gene deletions in *VHL*, respectively. These subtypes are associated with a lower risk of PPGL development (0.5–10%) (Nordstrom-O'Brien *et al.* 2010, Lomte *et al.* 2017). VHL type 2a, b and c are caused by missense mutations in *VHL* and associated with >60% risk of PPGL development (Chen *et al.* 1995, Zbar *et al.* 1996). The risk of PPGL is also reported to vary according to the type of missense mutation, with alterations leading to amino acid changes on the surface of pVHL associated with a higher risk of PPGL when compared to mutations that occur deep within pVHL (Ong *et al.* 2007).

PPGL develop in approximately 10–20% of patients with VHL, with the earliest reported cases from age 2 years and a mean age of onset of 20–25 years (Neumann *et al.* 2002, Sovinz *et al.* 2010, Bholah & Bunchman 2017). Approximately 90% of PPGLs are located within the adrenal glands (Walther *et al.* 1999b), 67–90% of which present bilaterally or multifocally (Walther *et al.* 1999b, Lomte *et al.* 2017). VHL is an autosomal dominant syndrome that is caused by germline pathogenic variants in *VHL*, encoding a protein with the same name (pVHL). pVHL is involved in the ubiquitination and degradation

of the hypoxia inducible factor (HIF), which plays a role in the regulation of gene expression. The prevalence of VHL ranges between 1/36,000 and 1/85,000 (Maher *et al.* 1991, Maddock *et al.* 1996). Approximately 80% of children have an affected parent, whereas 20% result from *de novo* mutations in *VHL* (Richards *et al.* 1995). Missense mutations account for approximately half of the identified germline pathogenic variants in *VHL*, followed by frameshift mutations, large deletions, nonsense mutations, splice-site mutations and in-frame deletions/insertions (Nordstrom-O'Brien *et al.* 2010). By age 18 years, 70% of VHL carriers develop at least one manifestation of the disease, reaching 87% by age 60 years (Binderup *et al.* 2017, Launbjerg *et al.* 2017).

McCune-Albright syndrome

McCune-Albright syndrome (MAS) describes the association of polyostotic fibrous dysplasia, café-au-lait macules, precocious puberty and overactive endocrinopathies. Affected individuals also were found to have an increased predisposition of Cushing syndrome in the infantile period from nodular adrenal hyperplasia. The genetic defect is due to a postzygotic gain-of-function point mutations in *GNAS*, within exon 8 of the Gsα subunit, which leads to constitutive activation of adenyl cyclase (Weinstein *et al.* 1991). Clinical manifestations of MAS are highly variable and depend on the distribution of somatic mosaic mutations in the various affected tissues. Patients with MAS may also present with non-functional ACAs at any age (Carney *et al.* 2011).

Thyroid tumours

Classification and molecular features

Benign thyroid masses are the most frequent thyroid neoplasms in young patients and include single thyroid nodules (not discussed in this review) and multinodular goitre (MNG). While MNG is frequent in adults, especially in the iodine-deficient population (Garcia-Garcia *et al.* 2017), it represents approximately 20% of benign thyroid masses in children often in the context of a positive family history of thyroid disease (Divarci *et al.* 2017).

Thyroid cancers account for ~3% of all malignancies in patients aged <20 years, 75% of which develop in the 15- to 19-year age group (Horner *et al.* 2009). Malignant neoplasms of the thyroid gland can be divided into two main categories: medullary thyroid carcinoma (MTC) originating from neural crest-derived calcitonin-producing C cells and non-medullary thyroid carcinoma

(NMTC) derived from thyroid follicular cells. The latter is further divided into papillary (PTC) and follicular (FTC) thyroid carcinomas, referred to as differentiated thyroid carcinomas (DTCs). PTC presents with several variants, altogether comprising 80–90% of all thyroid cancers (Davies & Welch 2006). Poorly differentiated and anaplastic thyroid cancers account for a small portion of NMTCs. While MTCs represent only 8% of thyroid malignancies in children and adolescents, they are the most frequent subtype to develop in the first 5 years of life, with a steady decline in incidence with advancing age (Dermody *et al.* 2016). Childhood cancer survivors are at higher risk of developing thyroid cancer, especially when exposed to therapeutic ionising radiation (Cardis *et al.* 2005). Currently, thyroid cancer represents ~10% of all second malignant neoplasms in this population.

While it is well established that thyroid carcinogenesis is the predominant feature of multiple endocrine neoplasia syndromes type 2, in the past decade, thyroid neoplasms and non-neoplastic pathology, such as goitre, have been progressively recognised as being part of numerous other cancer susceptibility syndromes, especially when occurring in younger patients. DICER1 syndrome is now clearly associated with MNG development in children and young adults. Although most DTCs are thought to arise through non-Mendelian mechanisms even in children, PTEN hamartoma tumour syndrome (PHTS), familial adenomatous polyposis (FAP), CNC, Werner and DICER1 syndromes should now be part of the differential diagnosis in a child with a thyroid mass. Non-syndromic forms of familial NMTCs are also responsible for 5% of NMTC cases. Approximately 25% of patients with apparently sporadic MTCs carry an activating germline point mutation in the *RET* gene that is associated with MEN type 2A, 2B and familial MTC (variant of MEN 2A). The finding of a germline pathogenic variant or the recognition of familial thyroid cancer enables the implementation of tumour surveillance strategies and appropriate family counselling. Progress in molecular diagnostic technology has permitted the transition from DNA linkage in the 1990s to direct mutation analysis (Fig. 1) allowing more efficient testing and rapid implementation of surveillance and preventive strategies, the latter proven to decrease mortality in patients with MEN2.

While it is widely accepted that MTC and NMTC present with distinct clinical and pathological features, the study of the somatic landscape of thyroid tumours have led to further understanding of their altered

Table 2 Somatic alterations in thyroid tumours.

Somatic alterations	PTC	FTC	PDTC/ATC	MTC	Examples of targeted agents for the treatment of thyroid carcinoma
RAS/MAPK pathway <i>RET</i> mutations	–	–	–	95% (Ped)	Vandetanib; kinase inhibitor targeting <i>RET</i> -tyrosine kinase
<i>RAS</i> (<i>NRAS</i> , <i>HRAS</i> , <i>KRAS</i>)	10–30%	30–50%	20–50% (PD) 10–40% (A)	25%	Tipifarnib; <i>RAS</i> inhibitor in phase II trials for thyroid tumours with <i>HRAS</i> mutations
<i>BRAF</i>	60–80% (adult) <20% (ped) ^a	15%	10–35% (PD) 10–50% (A)	–	Vemurafenib; <i>BRAF</i> inhibitor used for PTC refractory to radioactive iodine
<i>RET</i> fusions	12%	–	–	–	BLU-667, <i>RET</i> inhibitor evaluated in a phase 1 trial
<i>NTRK 1,3</i> fusions	2–15%*	–	–	–	Larotrectinib; pan- <i>TRK</i> inhibitor under investigation in thyroid cancer
<i>ALK</i> fusions	1–7%	–	0–10%	–	Ceritinib, <i>ALK</i> inhibitor under investigation in ATC in patients with <i>ALK</i> alterations
<i>AKAP6-BRAF</i>	11%	–	–	–	–
PI3K-AKT pathway <i>PIK3CA</i>	–	<10%	2–10% (PD) 10–20% (A)	–	CUDC-907, a dual inhibitor of <i>HDAC</i> and <i>PI3K</i> signalling under investigation for thyroid cancer
<i>AKT1</i>	–	–	5–10%	–	AZD-5363, <i>AKT</i> inhibitor under investigation in patients with <i>AKT</i> mutations
<i>PTEN</i>	–	<10%	5–20% (PD) 10–15% (A)	–	<i>PI3KB</i> inhibitor GSK-2636771 in patients with <i>PTEN</i> mutations
WNT pathway <i>CTNNB1</i>	–	–	10–20% (PD) 5–60% (A)	–	–
<i>TERT</i> promoter	5–15%	10–35%	20–50% (PD) 30–75% (A)	–	–
Other chromosome rearrangements and point mutations <i>PAX8-PPARG</i>	–	30–50%	–	–	Efatutazone dihydrochloride, <i>PPARG</i> agonist investigated for anaplastic thyroid cancer
<i>TP53</i>	–	–	20–30% (PD) 50–80% (A)	–	–
<i>DICER1</i>	10%	–	–	–	–
<i>PRKAR1A</i>	~0.2% (amplified)	–	–	–	–

Adapted from: Rosenbaum *et al.* 2005, Sassolas *et al.* 2012, Xu & Ghossein 2016, Dom *et al.* 2018, Giordano 2018, Wasserman *et al.* 2018.

*15% of radiation induced PTCs; ^aprevalence of *BRAF* mutations increases with age.

A, anaplastic; FTC, follicular thyroid carcinoma; PD, poorly differentiated; PDTC/ATC, poorly differentiated thyroid carcinoma/anaplastic thyroid carcinoma; PTC, papillary thyroid carcinoma; MTC, medullary thyroid carcinoma.

molecular pathways and tumourigenic drivers, allowing the integration of targeted therapy in some cases (Roskoski & Sadeghi-Nejad 2017), especially in aggressive forms of MTC. Numerous somatic changes occur in NMTC and differ according to thyroid cancer histology, presumed aetiology and age group. Table 2 summarises the main somatic changes identified in thyroid tumours and examples of their clinical implications in terms of treatment (Rosenbaum *et al.* 2005, Sassolas *et al.* 2012, Xu & Ghossein 2016, Dom *et al.* 2018, Giordano 2018, Wasserman *et al.* 2018).

Familial syndromes

DICER1 syndrome

Numerous reports have described young patients carrying germline *DICER1* pathogenic variants with thyroid disease, mostly MNG. Nodular thyroid disease is the most frequent clinically recognised thyroid feature in *DICER1* syndrome carriers, which predisposes to thyroid malignancy (Khan *et al.* 2017b). The cumulative incidence of MNG or thyroidectomy in female carriers of *DICER1* pathogenic variants reaches 23% at 20 years and 50–75%

by 40 years. In males, the cumulative incidence of MNG remains between 10 and 14% by 40 years (Khan *et al.* 2017b). DTC of the papillary and follicular subtypes have also been reported in children with DICER1 syndrome (de Kock *et al.* 2014b). Most of these patients had received chemotherapy and/or radiation as part of treatment of a previous tumour, which has led to the postulation of a potential link between DTC development and chemo- and radio-therapeutic agents. However, one family with several children diagnosed with DTC without previous exposure to chemotherapy was reported (Rutter *et al.* 2016). It is estimated that germline *DICER1* pathogenic variant carriers have a 16- to 18-fold risk of developing DTC compared to non-carriers (Khan *et al.* 2017b). In the setting of *DICER1* syndrome, thyroid ultrasound with assessment of regional lymph nodes should be initiated at the age of 8 years, and if normal, repeated every 3 years (Schultz *et al.* 2017). *DICER1* syndrome is an autosomal dominant syndrome that is caused by germline pathogenic variants in the *DICER1* gene, encoding the *DICER1* protein, which is a member of the ribonuclease (RNase) III family of proteins. This protein is responsible for cleaving non-coding small RNA precursors (pre-miRNA) to generate mature miRNAs that are involved in posttranscriptional regulation of gene expression (Krol *et al.* 2010). Heterozygotes for germline *DICER1* pathogenic variants are predisposed to a variety of benign and malignant tumours including pituitary blastoma, a rare but aggressive brain tumour (Table 1). These *DICER1*-related neoplasms typically harbour a characteristic somatic mutation within the RNase IIIb domain of *DICER1* (Heravi-Moussavi *et al.* 2012, de Kock *et al.* 2013). Macrocephaly (head circumference >97th perc) has been reported in *DICER1* patients (Khan *et al.* 2017a) and may be a clinical clue to the diagnosis. This is also a typical and even more pronounced clinical feature for *PTEN* hamartoma tumour syndrome, which is also linked to thyroid tumour development.

***PTEN* hamartoma tumour syndrome**

Thyroid malignancy may be the first recognised feature of PHTS in children (Smith *et al.* 2011). PHTS is a group of genetic conditions caused by germline pathogenic variants in the *PTEN* tumour suppressor gene, with several overlapping clinical phenotypes including Cowden, Cowden-like, Bannayan-Riley-Ruvalcaba, Proteus and Proteus-like syndromes. *PTEN* encodes a dual specificity phosphatase, involved in the phosphatidylinositol 3-kinase pathway. In germline *PTEN* carriers, abnormal

thyroid gland pathology is reported in 75% of patients, whereas thyroid cancer is in 14–24% (Ngeow *et al.* 2011, Cameselle-Teijeiro *et al.* 2015). Multifocality, bilaterality and pathological findings in thyroid tumour specimens such as the presence of adenomatous nodules, microadenomas, a background of lymphocytic thyroiditis and *PTEN*-negative immunostaining are clues for PHTS. The predominant histological subtypes are PTC (60–80%), FTC (14–45%) and anaplastic thyroid cancer (6%). In one multicentre study, 16.7% of patients with Cowden or Cowden-like syndromes developed thyroid cancer under the age of 18 years (4 PTC, 1 FTC, 1 Hürthle cell carcinoma), with the earliest reported case at the age of 7 years, equivalent to a nine-fold risk of paediatric-onset thyroid carcinoma in *PTEN* carriers (Ngeow *et al.* 2011). FTC is considered a major diagnostic feature of PHTS. The median age at diagnosis of thyroid cancer in the overall *PTEN* mutation-positive Cowden or Cowden-like syndrome cohort was 37.5 years, with a female-to-male ratio of 2.5 to 1. Another study showed that 0.8% of consecutive patients with any type of DTC, unselected for age, personal or family history, had a germline pathogenic variant in *PTEN* (Nagy *et al.* 2011), both of which had FTC and macrocephaly, while *PTEN* pathogenic variants were not identified in any of the 402 adults tested in the Cancer Genome Atlas dataset (PMID 25417114, 27959678). Other clinical features suggestive of PHTS are presented in Table 1. Of note, the first manifestations of PHTS in the paediatric age may greatly differ from adult presentations of this syndrome. Macrocephaly, autistic features and developmental delay are recognised as suggestive features in children, while benign and malignant neoplasms account for the majority of the presenting features in adulthood.

Familial adenomatous polyposis

FAP syndrome is associated with the development of PTC, most notably, the cribriform-morular variant (CMV-PTC), accounting for <1% of thyroid tumours. Approximately half of patients who develop CMV-PTC are affected with FAP (Levy *et al.* 2014, Lam & Saremi 2017), while 36–73% of FAP-related PTCs have a CMV-PTC subtype (Feng *et al.* 2015, Uchino *et al.* 2016). Bilaterality and multicentricity are common features of CMV-PTC in the context of FAP. It is estimated that a third of patients are diagnosed concomitantly with PTC and FAP, a third with PTC and a third with FAP prior to the diagnosis of thyroid cancer. Clinically recognised PTCs develop in 0.4–2.3% of patients with FAP patients, with a

female-to-male ratio of 10:1 and occur most often in the first 2 decades (Cetta *et al.* 2000, Steinhagen *et al.* 2012). The actual prevalence is higher (2–12%), as suggested in studies involving thyroid ultrasound surveillance in patients with FAP (Herraiz *et al.* 2007). Germline pathogenic variants in *APC* in patients with PTCs are typically located in the 5' position of the gene, in the similar genomic area usually associated with congenital retinal pigment epithelial hypertrophy (between codons 457 and 1444) (Cetta *et al.* 2000, Kim *et al.* 2005). Adrenocortical tumours, such as ACC and PBMAH, have only been reported in adults with FAP (Jasperson *et al.* 1993). The risk of developing adrenal tumours in FAP is two to four times higher than the general population (Gaujoux *et al.* 2010, Berthon *et al.* 2012).

Werner syndrome

Werner syndrome, caused by biallelic loss-of-function pathogenic variants in *WRN*, is a recessively inherited condition associated with premature features of normal ageing starting in the second decade and the development of multiple cancer types including NMTC. It is estimated that half of persons with Werner syndrome develop at least 1 malignancy by age 40 years with the age range of the first neoplasm between 20 and 69 years (Lauper *et al.* 2013). In Werner syndrome patients residing in Japan, thyroid carcinoma represented up to 20% of the reported malignancies, with a striking FTC subtype predominance (Goto *et al.* 1996, Lauper *et al.* 2013). In contrast, thyroid carcinoma incidence rates were lower (6%) in patients residing outside of Japan, with no apparent predilection for FTC histology, suggesting a genotype–phenotype difference (Ishikawa *et al.* 1999). The median age for thyroid carcinoma diagnosis in patients with Werner syndrome is 40 years (range 25–46 years), with no paediatric-reported cases.

Familial non-medullary thyroid carcinomas

Non-syndromic familial non-medullary thyroid carcinomas (FNMTCs) is typically defined by 2 or more first-degree family members affected by thyroid carcinoma without an underlying known syndrome and accounts for to 2.5–10.5% of all follicular cell origin thyroid cancers (Nose 2008, Bonora *et al.* 2010). Due to the high prevalence of thyroid cancer, in approximately half of families who have 2 affected members, the association is simply because DTC is not rare and is not attributable to shared genetic factors (Alsanea & Clark 2001). Familial

papillary and Hürthle cell thyroid carcinomas are the predominant subtypes of FNMTC. Younger age of onset, tumour multifocality, bilaterality, lymph node metastasis and extra-thyroidal extension are features of FNMTC (Capezzone *et al.* 2008, Nose 2008). Furthermore, benign thyroid parenchymal and nodular diseases are often associated with FNMTC (Alsanea & Clark 2001). Thyroid carcinomas, in the context of FNMTC, behave more aggressively than sporadic forms with poorer survival rates (Alsanea *et al.* 2000, Capezzone *et al.* 2008). FNMTC remains a diagnosis in which the genetic basis has not clearly been identified and requires further research. Numerous susceptibility genes have been described in association with FNMTC, such as *HABP2* (Gara *et al.* 2015), *FOXE1* (Pereira *et al.* 2015), *TITF-1/NKX2.1* (Ngan *et al.* 2009), although none have been firmly established as causal drivers of the disease.

Familial syndromes associated with medullary thyroid carcinoma

MEN2 syndromes are characterised by a striking predisposition to early-onset MTC with or without PPGL and primary hyperparathyroidism (pHPT) and have an estimated prevalence of 1/35,000 (DeLellis *et al.* 2004). Germline activating mutations in the *RET* (Rearranged during transfection) proto-oncogene (10q11.2) have been found in 98% of patients affected with MEN2. *RET* encodes a receptor tyrosine kinase that is activated by the glial-derived neurotrophic factor (GDNF) family of ligands and is involved in signal transduction and activation of the MAPK and other signalling pathways that promote cell growth and survival. It is expressed in neuroendocrine cells such as thyroid C cells and adrenal medullary cells, neural cells, urogenital tract cells and germ cells of the testis (Santoro *et al.* 2004, Wells & Santoro 2009). Over 100 distinct germline pathogenic variants of the *RET* gene have been identified in patients with hereditary MTC. Molecular categorisation of *RET* germline variants has become clinically relevant as genotype–phenotype correlations are clearly established, with the type of *RET* mutation and the underlying mode of RET receptor activation affecting the timing of MTC development. *RET* mutations are classified as moderate, high or very high risk for MEN2.

Over 90% of patients with MEN2 syndromes will develop MTC over a lifetime, with it being the most common cause of mortality in patients with multiple endocrine neoplasia type 2A (MEN2A), FMTC and MEN2B.

MEN2A and familial MTC

MEN2A and its variant, familial medullary thyroid carcinoma (FMTC), are autosomal dominant conditions caused by germline activating mutations in *RET*, typically located in the cysteine residues of the extracellular region of the RET protein (Cys 609, 61, 618, 629 and 634) (Eng *et al.* 1996, Moers *et al.* 1996). MEN2A is clinically characterised by the development of MTC (90–95%), PPGL (50%), pHPT (20–30%) and by non-malignant features (Table 1) (Eng *et al.* 1996). Clinical manifestations of MTC are rarely observed in MEN2A carriers in the first decade of life; the prevalence increases with age, ~25% at 13 years and ~70% at 70 years. By age 35 years, nearly all patients with MEN2A who have not had thyroidectomy will have biochemical evidence of MTC. In contrast, MTC onset often occurs past the 2nd and 3rd decades of life in patients with FMTC. In carriers of MEN2A, timing of prophylactic thyroidectomy can be guided by the patient's genotype and calcitonin levels. In children with 'high risk' alleles, such as mutations in codons 634 and 883, thyroidectomy, often without the need for cervical lymph node dissection, can be achieved by age 5 years or sooner if there is presence of clinical or radiological signs or rising serum calcitonin levels are appreciated (Wasserman *et al.* 2017, Wells 2018). PPGL may also be the first recognised feature of MEN2A in 13–27% of cases. Mutations in codon 634 have been associated to a higher incidence of PPGL and pHPT (Eng *et al.* 1996, American Thyroid Association Guidelines Task Force 2009).

Multiple endocrine neoplasia type 2B

Patients affected with MEN2B have either inherited a pathogenic *RET* variant in an autosomal dominant manner (50%) or have acquired a *de novo* *RET* alteration (50%). As there is such a high *de novo* mutation rate, a family history of thyroid cancer is often absent, contributing to a late diagnosis of MTC associated with a higher likelihood of metastatic disease and decreased survival. In MEN2B, the onset of MTC is often in the first year of life. A classic p.M918T mutation located within the substrate-binding pocket of the intracellular tyrosine kinase domain of the *RET* gene is identified in 98% of patients with MEN2B (Wells *et al.* 2015). This mutation is considered a 'very high risk' genotype leading to a highly penetrant disease with nearly 100% likelihood of developing an aggressive form of MTC in early childhood and 50% risk of developing pheochromocytomas, often with bilateral or multifocal features. For patients with MEN2B, especially those with the classic p.M918T mutation, a total thyroidectomy is

recommended in the first year of life, preferably achieved by a surgeon with experience with MEN disorders (Wells *et al.* 2015). MEN2B-associated features are described in Table 1.

When a child develops an MTC, independently of family history or tumour characteristics, a referral to a medical genetics service should be part of the short-term management. The presence of multifocal and/or bilateral disease, early age of onset of tumour development or evidence of C-cell hyperplasia are clues to the presence of an underlying CPS. Multicentric and bilateral MTC is observed in 30% of sporadic cases and nearly 100% of hereditary cases. In families affected with any of the MEN2 syndromes, predictive genetic testing is recommended at childhood, at birth in the case of MEN2B, and before age 5 years in MEN2A or FMTC. MEN2 syndromes are one of the few CPSs with proven preventive measures, associated with improved survival rates and decreased mortality. Genotype–phenotype correlations in the *RET* gene have influenced timing of thyroidectomy in patients with MEN2 (Wasserman *et al.* 2017).

Parathyroid tumours

Classification and molecular features

Parathyroid adenomas and carcinomas are rare neoplasms in children and adolescents and are most often diagnosed in the evaluation of hypercalcaemia. Approximately 70–90% of cases of pHPT in children are caused by parathyroid adenomas while <1% of cases are associated with parathyroid carcinomas. Parathyroid carcinomas usually develop in the 4th or 5th decade of life with no gender predilection, whereas parathyroid adenomas typically present at an older age and have a female predominance of 3:1. Parathyroid adenomas and carcinomas are characteristically difficult to distinguish on histology, with features such as local invasion and presence of metastatic disease contributing to the final diagnosis (Delellis 2008). It is estimated that >10% of apparently sporadic parathyroid tumours are associated with an underlying CPS, namely hyperthyroidism–jaw tumour syndrome (HPT-JT), familial isolated hyperparathyroidism (FIHP), MEN1, MEN2A and MEN4 (Belcher *et al.* 2013, Thakker 2016).

Loss of 11q and somatic mutations in *MEN1*, encoding menin, are the most characteristic findings in parathyroid adenomas, with biallelic inactivation of *MEN1* identified in up to 35% of cases (Newey *et al.* 2012). *CCND1*, encoding cyclin D1, is also considered as a driver

mutation in parathyroid adenomas. Overall, 20–40% of parathyroid adenomas have overexpression of cyclin D1, caused by *PTH-CCND1* rearrangements (8% of cases) or DNA amplification (Vasef *et al.* 1999, Westin *et al.* 2009). Similarly, Cyclin D1 is overexpressed in most parathyroid carcinomas (Vasef *et al.* 1999). Other contributors to parathyroid tumourigenesis include *CDKN1B*, *CDKN1A*, *CDKN2B*, *CDKN2C*, *CTNNB1* and *LRP5* although their level of involvement requires further studies. Epigenetic alterations including hypermethylation of *RIZ1*, *APC*, *RASSF1A* and *HIC1* have been recently described in parathyroid adenomas, but their significance remains unclear (Costa-Guda & Arnold 2014).

The identification of somatic gene alterations in various benign and malignant forms of neoplasms has been instrumental in understanding the malignant transformation ability of benign tumours, through progression modelling. In these models, early genetic alterations should be found equal or at higher rates as the tumour progresses to a malignant form. *MEN1* mutations are found in up to 35% of parathyroid adenomas and are not identified in parathyroid carcinomas, which suggest that parathyroid adenomas and carcinomas are distinct entities (Farnebo *et al.* 1998, Costa-Guda *et al.* 2013). In contrast, progression from parathyroid adenoma to carcinoma has been described in patients with germline pathogenic variants in *HRPT2* (Costa-Guda & Arnold 2014). Sporadic forms of parathyroid carcinoma harbour somatic *HRPT2* mutations, encoding parafibromin, in two-thirds of cases and are very rare in parathyroid adenomas (Shattuck *et al.* 2003).

Familial syndromes

Multiple endocrine neoplasia type 1

MEN1 is an autosomal dominant syndrome due to heterozygous inactivating germline pathogenic variants of the tumour suppressor gene *MEN1* (Chandrasekharappa *et al.* 1997). Pathogenic alterations in *MEN1* are found in approximately 90% of affected individuals with variable expression with age. The disease prevalence has been estimated at 1/30,000 (Agarwal 2013). Clinical features include the triad of pHPT due to parathyroid hyperplasia (>95%), pituitary adenomas (45%) and neuroendocrine tumours (>30%). Non-functional adrenocortical tumours are not uncommon in MEN1 (Thakker *et al.* 2012). Gatta-Cherifi *et al.* reported adrenal enlargement in 20.4% (146/715) of patients with MEN1, due to macronodular ACT (10.1% of the cohort) (Gatta-Cherifi *et al.* 2012). Of the functional ACT,

primary aldosteronism and adrenal Cushing syndrome predominates (Gatta-Cherifi *et al.* 2012, Simonds *et al.* 2012). Other manifestations of MEN1 are included in Table 1.

Approximately 12% of MEN1 patients are diagnosed with the disease in the first 2 decades of life (Goudet *et al.* 2010). pHPT is the earliest recognised feature in patients with MEN1, with the youngest reported cases at age 4 and 8 years (Goudet *et al.* 2015). In a study evaluating the clinical features of 122 children with MEN1 aged <21 years, 75% had pHPT (Goudet *et al.* 2015).

Multiple endocrine neoplasia type 4

It is estimated that 3% of *MEN1*-negative patients with MEN1 phenotype harbour heterozygous germline loss-of-function *CDKN1B* mutations, encoding for the cyclin-dependent kinase inhibitor p27^{Kip1}, which plays a role in cell cycle interactions. Homozygous pathogenic variants in *CDKN1B* were initially identified in a murine model displaying MEN1-like features, which led to the study in humans, linking heterozygous *CDKN1B* mutations to MEN4, the most recent form of MEN (Pellegata *et al.* 2006). While recessively inherited in rats, this condition was found to be autosomal dominant in humans or acquired sporadically. MEN4 is characterised by the development of parathyroid adenoma and anterior pituitary tumours. pHPT is a key feature present in approximately 80% of known cases of MEN4, with a later age of onset than that seen in MEN1 (mean 56 vs 25 years) (Lee & Pellegata 2013, Alrezk *et al.* 2017). The youngest described case was in a 15-year-old who manifested with symptomatic pHPT (Alrezk *et al.* 2017). Germline pathogenic variants in *CDKN1B* also predispose to NET, adrenocortical tumours, neoplasms of the kidney, ovary, thyroid and meninges in adults (Alrezk *et al.* 2017). MEN4 is a clear example of the progress of genomic medicine as demonstrated by the decreased latency period between the linkage of a *CDKN1B* to this distinct clinical phenotype. (Fig. 1).

Hyperparathyroidism-jaw tumour syndrome and familial isolated hyperparathyroidism

Hyperparathyroidism-jaw tumour syndrome (HPT-JT) and familial isolated hyperparathyroidism (FIHP) are caused by germline pathogenic variants in the *CDC73* tumour suppressor gene encoding parafibromin (Carpten *et al.* 2002). While FIHP is uniquely associated with pHPT, HPT-JT can also lead to the development of fibro-osseous jaw tumours (25–50%), renal cysts or tumours (15%) and uterine fibromas (75% of females) (Jackson *et al.* 1990,

Parfitt *et al.* 2015). Parathyroid tumours develop in >90% of patients with HPT-JT, 15% of which are parathyroid carcinoma (Jackson *et al.* 1993, Kutcher *et al.* 2013). The median age of pHPT diagnosis is 27 years and can occur as young as 7 years (Pichardo-Lowden *et al.* 2011, Bricaire *et al.* 2013). Current recommendations support the initiation of tumour surveillance including biochemical screening for pHPT between the ages of 5 and 10 years (Wasserman *et al.* 2017). In contrast to other genetic conditions, isolated parathyroid adenomas are more often seen than multifocal disease. Approximately 75% of patients with HPT-JT harbour germline pathogenic variants in the coding region of *CDC73*, and a smaller proportion of *CDC73* negative cases may be related to anomalies in the *CDC73* promoter region, non-coding regions or large deletions that could be missed with standard sequencing methods. These conditions are inherited in an autosomal dominant fashion with incomplete penetrance.

Pituitary tumours

Classification and molecular features

Adenohypophysis consists of a heterogeneous population of well-differentiated hormone-secreting cells, including somatotrophs, lactotrophs, mammosomatotrophs, corticotrophs, thyrotrophs and gonadotrophs (Watkins-Chow & Camper 1998). Approximately ~3.5-6% of all surgically treated paediatric pituitary tumours arise from this region (Kane *et al.* 1994). Paediatric pituitary adenomas are often benign with the most frequently encountered tumours being prolactinomas (most are in adolescents), followed by corticotropinomas and somatotropinomas (Lafferty & Chrousos 1999). Paediatric nonfunctioning pituitary adenomas are encountered in 3-6% of all cases (Partington *et al.* 1994, Mindermann & Wilson 1995). It is now well established that known underlying germline defects cause approximately one-fifth of pituitary adenomas in children and adolescents. Pituitary blastoma, a rare tumour of the pituitary gland classically presenting in the first two years of life, can be initially mistaken for a pituitary adenoma. These tumours are strongly associated with *DICER1* syndrome, as described above. Germline pathogenic variants in *DICER1* were identified in 90% of cases in one study, and is considered a pathognomonic feature of *DICER1* syndrome (de Kock *et al.* 2014a). In this section, we will focus on the genetics of Cushing disease, gigantism and acromegaly.

Cushing disease

Cushing disease (CD) is an extremely rare paediatric condition with an incidence of 1.2-1.7 cases per million per year (Lindholm *et al.* 2001) that arise from monoclonal proliferation of corticotrophs leading to endogenous ACTH-dependent hypercortisolemia. Paediatric Cushing syndrome is not clinically distinguishable from adult-onset forms except for the height deceleration. Other clinical features include weight gain, headaches, hypertension, glucose intolerance, and gonadal dysfunction (Lodish *et al.* 2018). Additionally, children and younger adolescents do not typically report problems with sleep disruption, muscle weakness, memory or cognition (Stratakis 2018). The risk for persistent and recurrent CD is higher among children of minority ethnic groups. (Gkourogianni *et al.* 2017).

Genetic alterations in corticotropinomas rarely occur in the known proto-oncogenes or tumour suppressor genes (Table 1) (Hernandez-Ramirez & Stratakis 2018). In contrast with other pituitary tumour types, the genetic causes of corticotropinomas are largely unknown. Recent studies have shown that the most common genetic alteration found in over one-third of paediatric corticotropinomas were recurrent activating somatic heterozygous driver mutations located in a hotspot region in exon 14 of the ubiquitin-specific protease 8 gene (*USP8*; chromosome 15q21.2) (Reincke *et al.* 2015, Faucz *et al.* 2017). Patients with CD harbouring mutations in *USP8* were older at diagnosis with a higher likelihood of recurrence when compared with patients without mutations (Faucz *et al.* 2017). Moreover, *USP8* mutations lead to activation of epidermal growth factor receptor (EGFR) signalling, a potential target for CD treatment. Recently, our group has identified 4 potentially pathogenic missense germline variants in *CDK5* and *ABL1* enzyme substrate 1 (*CABLES1*; chromosome 18q11.2), a tumour suppressor gene that regulates cell cycle progression. Genetic alterations in *CABLES1* were found in 4 female patients (2 young adults and 2 children) with large corticotropinomas that were difficult to manage (Hernandez-Ramirez *et al.* 2017). Other somatic events reported in CD with aggressive behaviour include genetic alterations in *p53* (chromosome 17p13.1) tumour suppressor gene (Kawashima *et al.* 2009).

Multiple endocrine neoplasia

MEN1 (Rix *et al.* 2004), *MEN2A* (Kasturi *et al.* 2017), *MEN2B*, and *MEN4* predispose to corticotropinoma formation. In one study of 74 patients with sporadic CD and 4 patients with syndromic CD, pathogenic variants in *MEN1* were only identified in 2 syndromic

patients with genetically confirmed MEN1 relatives (Stratakis *et al.* 2010), providing evidence for the role of this gene in corticotroph tumourigenesis. Pituitary adenomas are the second most common phenotypic feature of MEN4, affecting ~37% of the reported cases with an age of diagnosis of 30-79 years (Alrezk *et al.* 2017). CD has been reported in only one adult with MEN4 due to a heterozygous 19-bp duplication (c.59_77dup19) in *CDKN1B*, leading to a truncated protein (Georgitsi *et al.* 2007), and none in paediatric cohorts with CD (Igreja *et al.* 2009, Stratakis *et al.* 2010).

Carney complex

In CNC, previous investigations did not reveal somatic or germline pathogenic variants in *PRKAR1A* in paediatric CD (Stratakis *et al.* 2010). Recently, our group reported a paediatric case of CD that was subsequently followed by PPNAD in a patient carrying an inactivating *PRKAR1A* pathogenic variant (Hernández-Ramírez *et al.* 2017), providing evidence for the role of *PRKAR1A* in corticotroph tumourigenesis.

Other syndromes

Other syndromes that predispose to Cushing disease include MAS (Weinstein *et al.* 1991, Riminucci *et al.* 2002), Tuberous Sclerosis (Nandagopal *et al.* 2007), and DICER1 syndrome (de Kock *et al.* 2014a, Sahakitrungruang *et al.* 2014). Familial isolated pituitary adenoma (FIPA), caused by germline pathogenic variants in *AIP*, has only rarely been associated with CD (Beckers *et al.* 2013).

Gigantism and acromegaly

Gigantism results from exposure of epiphyseal growth plates before their fusion to growth hormone, while acromegaly occurs after fusion of the plates. The most common pituitary pathology is a benign growth hormone-secreting pituitary adenoma, referred to as a somatotropinoma. The incidence of pituitary gigantism and acromegaly are approximately 8 and 11 cases per million person-years, respectively (Burton *et al.* 2016). The cyclic AMP pathway is frequently dysregulated in sporadic somatotropinomas; somatic activating mutations in *GNAS*, which encodes for Gsa, are found in the heterozygous state (Yasufuku-Takano *et al.* 1999), and on the maternal allele (Hayward *et al.* 2001), representing the first and largest somatic genetic alteration in somatotropinomas (Landis *et al.* 1989). Most cases of paediatric gigantism are familial.

X-linked acrogigantism

X-linked acrogigantism (X-LAG) is the most common cause of early childhood-onset gigantism that is seen in ~80% of pre-pubertal gigantism. X-LAG is caused by GH (and prolactin) over secretion due to a pituitary macroadenoma or hyperplasia (Trivellin *et al.* 2014), with a median age of onset of 12 months. Germline microduplications on chromosome Xq26.3 causing X-LAG mainly arise *de novo*. The culprit gene in this duplicated region is *GPR101*, which codes for an orphan G-protein coupled receptor (GPCR) (Trivellin *et al.* 2014, Beckers *et al.* 2015). In sporadic acromegaly, a rare missense variant in *GPR101* (p.E308D) was identified in approximately 4% of cases (Lecoq *et al.* 2016).

Other syndromes

Gigantism can occur in association with FIPA, McCune-Albright syndrome, MEN1, 3PA syndrome (association of familial PPGL and pituitary tumours due to a pathogenic variant in *SDHx*), NF1, and rarely in MEN4 (Thakker *et al.* 2012, Xekouki *et al.* 2012, Salenave *et al.* 2014, Hernandez-Ramirez *et al.* 2015, Rostomyan *et al.* 2015, Sambugaro *et al.* 2015, Alrezk *et al.* 2017, Hannah-Shmouni *et al.* 2017). Cambiaso *et al.* found GH excess in 7 (10.9%) out of 64 children with NF1 and optic pathway glioma (Cambiaso *et al.* 2017).

Summary

The identification of the genes responsible for the various CPSs in this review has enabled the genetic diagnosis and early identification of patients and their at-risk family members. Genetic testing in clinical practice for familial syndrome has become widely spread and considered routine in tertiary medical centres. Most paediatric CPSs are familial and rarely sporadic. When faced with a rare endocrinopathy in paediatrics, such as PPGL, Cushing disease or thyroid cancer, clinicians are encouraged to obtain a detailed family history and pedigree to deduce dominance and distinguish autosomal from X-linked inheritance. Pattern recognition, age of onset, radiological and histopathological features are key in distinguishing between the various CPSs. Thus, when a clinician encounters a paediatric patient with any of the syndromic features, genetic testing and counselling regardless of family history should be considered as many of these conditions may have decreased penetrance and first-degree relatives that are carriers may not be affected. A low threshold for exploring genetic testing is important

particularly if the clinical phenotype warrants it. Genetic counselling and testing strategies in the paediatric population are not without complexities and ethical challenges which need to be considered. Numerous recent publications and position statements have addressed these issues (Botkin *et al.* 2015, Botkin 2016, Newson & Schonstein 2016). Screening should also be offered to a first-degree relative when a germline pathogenic variant in a disease-causing gene has been identified. Additionally, the identification of a germline pathogenic variant should prompt periodic clinical, biochemical and radiological screening for the syndrome in question. Periodic reassessment of the medical literature and raw genetic data is encouraged to identify new genes or syndromes in individuals with a suspected syndrome and an unidentified genetic mutation.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Authors' contribution statement

C G and F H-S: implicated in all aspects of this review and co-wrote the manuscript; M K: contributed to the evidence-based literature review and conception of the tables/figures; W D F and C S: review conception and revision of manuscript.

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