Chapter 9
Diseases Predisposing to Adrenocortical Malignancy (Li–Fraumeni Syndrome, Beckwith–Wiedemann Syndrome, and Carney Complex)

Anne Jouinot and Jérôme Bertherat

Abstract Adrenocortical malignancies can occur in the context of several tumor predisposition syndromes.

The Carney complex (CNC) is responsible for the majority of primary pigmented nodular adrenal diseases and is more rarely associated with adrenocortical carcinoma (ACC). Other core manifestations of CNC include cardiac and cutaneous myxomas, lentiginosis, somatotroph pituitary adenomas, Sertoli tumors, melanocytic schwannoma, and thyroid, breast, and bone tumors. CNC is mostly due to germline inactivating mutations of *PRKAR1A*.

The majority of childhood ACC are related to genetic predisposition. The Beckwith–Wiedemann syndrome (BWS) is an overgrowth and tumor predisposition syndrome due to genetic or epigenetic alterations at the 11p15 locus. Classical tumor spectrum of BWS includes embryonal tumors and childhood ACC. The Li–Fraumeni syndrome (LFS) is a devastating tumor predisposition syndrome, due to germline inactivating mutations of *TP53*, and characterized by a high, various, and early-onset cancer risk. LFS spectrum includes premenopausal breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumor, and ACC, accounting for 50–80% of pediatric cases. Finally, germline predisposition affects up to 10% of adult ACC patients, mostly in part of LFS and Lynch syndrome.

This chapter focuses on the diagnosis, screening, and management of adrenal tumors in part of these tumor predisposition syndromes.

Keywords Carney complex · Beckwith–Wiedemann syndrome · Li–Fraumeni syndrome · primary micronodular adrenal hyperplasia · adrenocortical carcinoma

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Abbreviations

ACC	Adrenocortical carcinoma
APC	Adenomatous polyposis coli
BRCA2	Breast cancer 2
BWS	Beckwith–Wiedemann Syndrome
cAMP	Cyclic adenosine monophosphate
CDKN1C	Cyclin-dependent kinase inhibitor 1C
CNC	Carney complex
IC	Imprinting center
IGF2	Insulin-like growth factor 2
KCNQ1	Potassium voltage-gated channel subfamily Q member 1
KCNQ1OT1	KCNQ1 overlapping transcript 1
LFS	Li–Fraumeni syndrome
MEN1	Menin 1
MLH1	MutL Homolog 1
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSH	MutS protein homolog
MUTYH	MutY DNA glycosylase
NF1	Neurofibromin 1
NMD	Nonsense-mediated mRNA decay
PDE	Phosphodiesterases
PKA	Protein kinase A
PMS2	Postmeiotic segregation increased 2
PPNAD	Primary pigmented nodular adrenal disease
PRKACA	Protein kinase cAMP-dependent catalytic subunit alpha
PRKACB	Protein kinase cAMP-dependent catalytic subunit beta
PRKAR1A	Protein kinase cAMP-dependent regulatory subunit type 1 alpha
SDH	Succinate dehydrogenase
TP53	Tumor protein 53
UPD	Uniparental disomy

9.1 Introduction

Adrenocortical tumors can occur in the context of several germline genetic defects (Table 9.1). This chapter focuses on the Carney complex and predispositions to adrenocortical carcinoma (ACC). Historically, childhood ACC has been linked to Li–Fraumeni syndrome and Beckwith–Wiedemann syndrome. More recently, large-scale genomic characterization programs have expanded the number of tumor susceptibility syndromes: new susceptibility genes have been identified and associations with known non-endocrine tumor syndromes have been revealed. Overall, germline predisposition is found in 10% of adult ACC and in up to 80% of childhood ACC. This chapter

Table 9.1 Predispositions to adrenocortical tumors

Adrenocortical tumor	Germline alteration	Syndrome	Predisposition frequency
Adrenocortical carcinoma	11p15, *CDKN1C*	Beckwith–Wiedemann	Rare, childhood onset
	TP53	Li–Fraumeni	50–80% in children, 3–5% in adults
	MLH1, *MSH2*, *MSH6*, *PMS2*	Lynch	3–5%
	MEN1	Multiple endocrine neoplasia type 1	1%
	APC	Familial adenomatous polyposis	Very rare, case reports
	NF1	Neurofibromatosis type 1	Very rare, case reports
	PRKAR1A	Carney complex	Very rare, case reports
	MUTYH	*MUTYH*-associated polyposis	Very rare, case reports
	SDHC, SDHA	Hereditary pheochromocytoma and paraganglioma	Very rare, case reports
	BRCA2	Hereditary breast and ovarian cancer	Very rare, case report
Primary pigmented nodular adrenocortical disease	*PRKAR1A*	Carney complex	80%
	PDE11A, *PDE8B*, *PRKACA*, *PRKACB*		
Primary macronodular adrenal hyperplasia	*ARMC5*		20%
	GNAS	McCune–Albright syndrome	Rare, childhood onset
	MEN1	Multiple endocrine neoplasia type 1	Rare
	FH	Hereditary leiomyomatosis and renal cell carcinoma	Rare
	APC	Familial adenomatous polyposis	Rare

develops several aspects of patient care, from the clinical and molecular diagnosis to the screening and management of adrenal tumors in part of a predisposition syndrome.

9.2 Carney Complex

9.2.1 Definition and Prevalence

The Carney complex (CNC) is a rare tumor predisposition syndrome, which associates endocrine and non-endocrine tumors. The most frequent manifestations of CNC are cutaneous lentigines, myxomas, and ACTH-independent Cushing's syndrome due to primary pigmented nodular adrenocortical disease (PPNAD) (Stratakis et al. 1998). However, the spectrum and severity of manifestations and the age of first tumor onset differ between the patients, even within the same family. CNC is caused in the majority of cases by *PRKAR1A* inactivating mutations (Kirschner et al. 2000).

The prevalence of CNC is still unknown (Lodish and Stratakis 2016), with only several hundreds of patients reported so far (Bertherat et al. 2009). The diagnosis is commonly made in children or young adults, at a median age of 20 years (Stratakis et al. 2001; Bertherat et al. 2009).

9.2.2 Clinical Diagnosis and Indications of Genetic Testing

Since its first description by Carney in 1985 as "the complex of myxomas, spotty pigmentation, and endocrine overactivity" (Carney et al. 1985), various associations of clinical manifestations have been reported. The CNC spectrum has been expended to pituitary adenomas (mostly somatotrophs), thyroid tumors, testicular and ovarian lesions (especially large-cell calcifying Sertoli tumors), melanocytic psammomatous schwannomas, breast ductal adenoma, and osteochondromyxomas. Conversely, PPNAD can be the single manifestation of the disease, named in these cases isolated PPNAD. Isolated lentigines and isolated cardiac myxomas are described as well (Bertherat et al. 2009). Diagnostic criteria have been proposed in 2001 (Stratakis et al. 2001) (Table 9.2). The diagnosis of CNC is established in a proband with either (1) two or more suggestive clinical manifestations or (2) one of these manifestations and an affected first-degree relative or a germline pathogenic variant in *PRKAR1A* on the genetic testing. Therefore, any patient with one manifestation strongly suggestive of CNC, such as PPNAD, should be considered for genetic testing.

9.2.3 Molecular Diagnosis

Germline inactivating mutations in *PRKAR1A* are detected in 70% of patients with CNC and in 80% of those with familial presentation or Cushing's syndrome due to

Table 9.2 Diagnostic criteria for the Carney complex (Stratakis et al. 2001)

Major diagnostic criteria	Frequency (%)
1. Spotty skin pigmentation (lentiginosis) with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal mucosa)	70–77
2. Myxoma (cutaneous and mucosa)[a]	20–32
3. Cardiac myxoma[a]	32–53
4. Breast myxomatosis[a] or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis	20
5. Primary pigmented adrenocortical disease[a] or paradoxical positive response of urinary glucocorticosteroid excretion to dexamethasone administration during Liddle's test	26–60
6. Acromegaly due to GH-producing adenoma[a]	10–12
7. Large-cell calcifying Sertoli cell tumor[a] or characteristic calcification on testicular ultrasound	33–41
8. Thyroid carcinoma[a] or multiple hypoechoic nodules on thyroid ultrasound in a young patient	5–25
9. Psammomatous melanotic schwannomas[a]	8–10
10. Blue nevus, epithelioid blue nevus[a]	50
11. Breast ductal adenoma[a]	20
12. Osteochondromyxoma[a]	2
Supplementary criteria	
1.Affected first-degree relative	
2. Inactivating mutation of the *PRKAR1A* gene	

The diagnosis of Carney complex is made if the patient exhibits two of the major criteria or one of these and one of the supplementary criteria
[a]*After histological confirmation*

PPNAD (Cazabat et al. 2006; Bertherat et al. 2009). The *PRKAR1A* gene is located at the 17q22–24 locus and encodes the regulatory subunit 1α of the protein kinase A (PKA), a key component of the cAMP signaling pathway (Fig. 9.1). This pathway plays a major role in development, maintenance, and secretory activity of several endocrine glands. *PRKAR1A* is a tumor suppressor gene according to the Knudson theory: one allele is inactivated by a germline mutation and the second allele is inactivated at the somatic level. *PRKAR1A* defects lead to the activation of the cAMP/PKA pathway, which in turn increases cell proliferation and steroidogenesis (Groussin et al. 2002).

Mutations in *PRKAR1A* are spread along the exons and their flanking intronic sequences. Most mutations are considered as "private," identified in only one or few families. De novo mutations are found in 30% of patients and in most sporadic cases (Bertherat et al. 2009). In more than 80% of the mutations, the sequence change (nonsense, frameshift, or splice variants) leads to premature stop codon causing degradation of the mutant mRNA by nonsense-mediated mRNA decay (NMD). In this case, no mutant protein is produced. In the tumor, the loss of the second allele is frequently observed (Kirschner et al. 2000). Rarely, missense mutations, short in-frame insertions/deletions, or splice variants translate into a mutant protein with altered or truncated sequence. This defective mutant protein can exert a dominant-

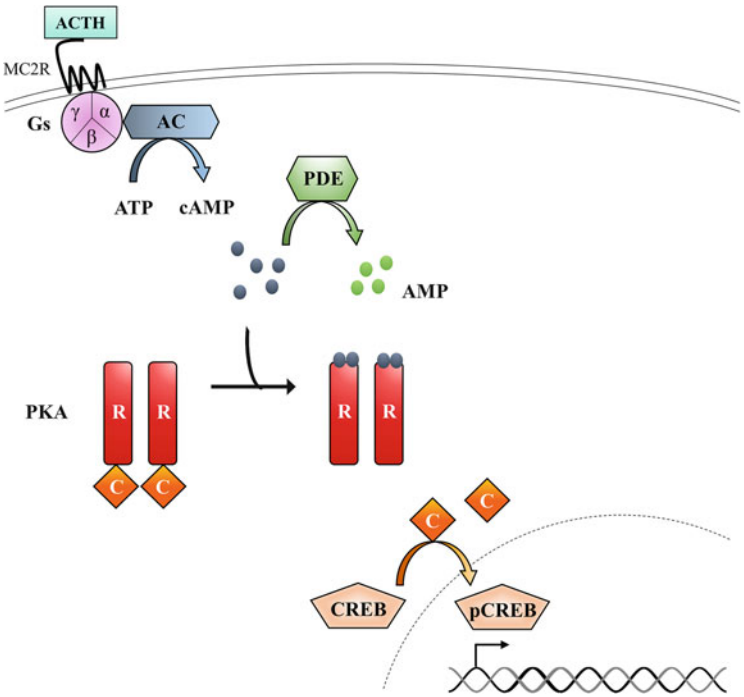

Fig. 9.1 cAMP/PKA signaling pathway in normal adrenal cortex. Adrenocorticotropic hormone (ACTH) stimulates the cAMP pathway after binding to the melanocortin 2 receptor (MC2R), a seven-transmembrane receptor coupled to Gs protein. The activated Gs protein activates the adenylyl cyclase enzyme (AC), which synthetizes cAMP. PKA is a hetero-tetramer formed by 2 regulatory subunits (R) and 2 catalytic subunits (C). The binding of cAMP to the regulatory subunits releases the catalytic subunits. The free catalytic subunits can phosphorylate several targets, including the transcription factor CREB (cAMP response element-binding protein), involved in steroidogenesis. The cAMP is degraded by the phosphodiesterases (PDE), which act as negative regulators of the pathway

negative effect over the wild-type protein. In this case, the somatic allelic loss of the wild-type allele is not always required (Groussin et al. 2002; Horvath et al. 2010).

Some genotype/phenotype correlations have been established (Bertherat et al. 2009). Patients with mutations that escape NMD and lead to a defective mutant protein exhibit a higher number of CNC manifestations. The hotspot mutation c.709 (−7–2)del6 is associated with PPNAD, while the other hotspot mutation c.491-492delTG is associated with cardiac myxomas, lentigines, and thyroid tumors. Exonic mutations are commonly associated with acromegaly, cardiac myxomas, lentigines, and schwannomas. Finally, patients harboring large deletions may present with severe phenotype, possibly as a result of haploinsufficiency of additional neighboring genes (Salpea et al. 2014; Stelmachowska-Banas et al. 2017). At the opposite, patients without *PRKAR1A* mutations show less myxomas and later-onset disease.

In addition to *PRKAR1A*, other genetic alterations in the cAMP/PKA signaling pathway have been reported, including *PDE11A* (Horvath et al. 2006; Libé et al. 2011) and *PDE8B* (Horvath et al. 2008; Rothenbuhler et al. 2012) inactivating

germline mutations and *PRKACA* (Beuschlein et al. 2014; Lodish et al. 2015) and *PRKACB* (Forlino et al. 2014) germline duplications. These alterations are mostly associated with isolated PPNAD.

9.2.4 Tumor Spectrum, Management, and Prognosis

The average life expectancy of patients with CNC may be reduced due to cardiac myxomas.

Cardiac myxomas are benign tumors, affecting 30–50% of CNC patients (Stratakis et al. 2001; Bertherat et al. 2009). These tumors can occur at a young age and in any or all cardiac chambers. They can cause severe cardiovascular complications, such as tumor emboli, cardiomyopathy, and arrhythmia. The only definitive treatment is surgery. Recent progress in this area has improved the morbi-mortality of CNC patients (Espiard and Bertherat 2013). Other sites for myxomas include the skin, breast, oropharynx, and female genital tract.

PPNAD is the most frequent endocrine manifestation of the CNC, reported in up to 60% of patients (Bertherat et al. 2009). Isolated PPNAD accounts for 12% of cases (Bertherat et al. 2009). Some patients developed a PPNAD during the first years of life, but the majority are diagnosed during the second and third decade (Stratakis et al. 2001) with a median age of 35 years. After puberty, a female predominance is observed (Bertherat et al. 2009). The usual treatment for patients harboring CS is the bilateral adrenalectomy (Powell et al. 2008). Histopathological examination reveals glands of normal size and weight or slightly enlarged, with multiple small (<10 mm) pigmented nodules around an atrophic cortex (Carney et al. 1985). Other adrenocortical tumors are rarely observed in CNC. Recently, two cases of adrenocortical carcinomas were described in patients affected by CNC. In both cases, a co-secretion of androgens and cortisol and a rapid occurrence of local recurrence and metastasis were observed (Anselmo et al. 2012; Bertherat 2012; Morin et al. 2012).

Other tumors include GH-producing adenomas in 10%, thyroid adenomas in 60%, melanotic psammomatous schwannomas in 10% of CNC patients, testicular tumors—mostly large-cell calcifying Sertoli tumors—in one-third of affected males, and ovarian serous cystadenomas in 14% of affected females.

Malignant tumors are rarely described in CNC: thyroid carcinomas and malignant schwannomas are reported in 3% and 1% of CNC patients, respectively (Stratakis et al. 2001; Bertherat et al. 2009).

Annual screening is recommended for CNC patients and at-risk relatives and includes at least echocardiography, testicular ultrasound, and measurements of urinary free cortisol and IGF-1 levels (Stratakis and Raygada 1993).

9.2.5 Risk of Recurrence and Genetic Counseling

CNC follows an autosomal dominant inheritance. The penetrance is almost complete (>95%) in patients with *PRKAR1A* mutations (Bertherat et al. 2009). After a

diagnosis of CNC in an index case, familial genetic testing should be proposed, along with tumor screening in presymptomatic predisposition carriers. In families with CNC where no genetic defect is identified, all at-risk family members are proposed to follow tumor surveillance protocols.

9.3 Beckwith–Wiedemann Syndrome

9.3.1 Definition and Prevalence

Beckwith–Wiedemann syndrome (BWS) is an overgrowth and tumor predisposition syndrome, recovering a great variability of phenotypes. Classical presentations include pre- and postnatal overgrowth, lateralized overgrowth (i.e., hemihypertrophy), macroglossia, visceromegaly, abdominal wall defects with exomphalos, and increased risk of embryonal tumors and adrenocortical cancer (Brioude et al. 2018). BWS is due to genetic or epigenetic alteration of the imprinted 11p15.5 region (Henry et al. 1989; Wilkin et al. 2000).

The diagnosis is commonly made in newborns or infants, with an estimated prevalence of 1 per 10–20,000 births (Mussa et al. 2013; Barisic et al. 2018). Familial presentations represent only 15% of BWS cases. The prevalence is influenced by neither gender nor ethnicity. A five- to tenfold increased risk of BWS is reported with assisted reproductive techniques (Mussa et al. 2017; Cortessis et al. 2018), as for other imprinting disorders.

9.3.2 Clinical Diagnosis and Indications of Genetic Testing

The first description of BWS was made more than 50 years ago (Wiedemann 1964). Several combinations of clinical features have been proposed for the diagnosis (Shuman et al. 1993; Weksberg et al. 2010), with macrosomia, macroglossia, and abdominal wall defects usually considered as major clinical features. However, some patients with 11p15.5 alteration do not display all these features (Ibrahim et al. 2014). Thus, additional definitions were proposed for “incomplete” or “atypical” BWS.

The recent consensus from the European Network for Congenital Imprinting Disorders defines instead the Beckwith–Wiedemann spectrum, which gathers a large range of phenotypes, from some individuals with only one suggestive clinical finding to the classical form of BWS (Brioude et al. 2018). Thus, Beckwith–Wiedemann spectrum encompasses three subsets: (1) classical BWS, (2) lateralized overgrowth syndrome, and (3) patients with 11p15.5 alteration who do not fit into these first two groups. A diagnostic score for Beckwith–Wiedemann spectrum is proposed, with cardinal clinical features scoring each 2 points, and suggestive clinical features scoring each 1 point (Table 9.3). Molecular testing of the 11p15 region is recommended for any patient with a score $\geq$ 2 points. Moreover, a score $\geq$ 4 points is retained for the diagnosis of classical BWS, even without confirmation of 11p15.5 alteration.

Table 9.3 Diagnostic criteria for the genetic testing of Beckwith–Wiedemann spectrum (Brioude et al. 2018)

Cardinal features (2 points per feature)
Macroglossia
Exomphalos
Lateralized overgrowth
Multifocal and/or bilateral Wilms tumor or nephroblastomatosis
Hyperinsulinism (lasting >1 week and requiring escalated treatment)
Pathology findings: adrenal cortex cytomegaly, placental mesenchymal dysplasia, or pancreatic adenomatosis
Suggestive features (1 point per feature)
Birthweight >2 standard deviation scores above the mean
Facial nevus simplex
Polyhydramnios and/or placentomegaly
Ear creases and/or pits
Transient hypoglycemia (lasting <1 week)
Typical Beckwith–Wiedemann tumors (neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumor, hepatoblastoma, adrenocortical carcinoma, or pheochromocytoma)
Nephromegaly and/or hepatomegaly
Umbilical hernia and/or diastasis recti

The diagnosis of the classical Beckwith–Wiedemann syndrome if the patient exhibits a score of ≥4 (this clinical diagnosis does not require the molecular confirmation of an 11p15 anomaly). Genetic testing is indicated in patients with a score of ≥2 (including those with a score of ≥4). Patients with a score of <2 do not meet the criteria for genetic testing

9.3.3 Molecular Diagnosis

BWS is associated with abnormal gene transcription due to molecular alterations within the imprinted 11p15.5 chromosome region. Genomic imprinting is an epigenetic phenomenon where genes are monoallelically expressed in a parent-specific manner. Imprinting centers (IC) are regions that can regulate the expression of imprinted genes in cis over a large distance. IC are characterized by differential DNA methylation of the parental alleles and are also referred to as differentially methylated regions (DMR).

The 11p15.5 region is divided into two functional domains, each harboring an independent IC (Fig. 9.2):

- The telomeric domain contains IC1 (also known as H19/IGF2:IG DMR) and regulates *H19* and *IGF2* expression. This domain is normally unmethylated on the maternal allele and methylated on the paternal allele.
- The centromeric domain contains IC2 (also known as KCNQ1OT1:TSS DMR) and regulates *KCNQ1OT1*, *KCNQ1*, and *CDKN1C* expression. This domain is normally methylated on the maternal allele and unmethylated on the paternal allele.

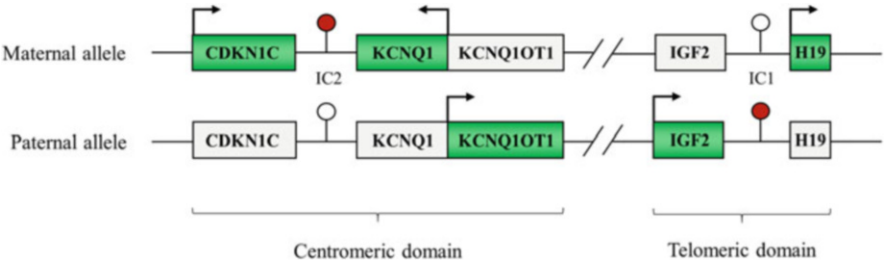

Fig. 9.2 The 11p15 region. The figure depicts the 11p15 locus with the imprinted genes and control regions that are implicated in the pathophysiology of Beckwith–Wiedemann syndrome. The two imprinted centers (IC)—IC1 on the telomeric domain and IC2 on the centromeric domain—are inversely methylated on maternal and paternal allele and result in opposite patterns of gene expression. On the maternal allele, the unmethylation of IC1 is associated with *H19* transcription and *IGF2* repression, and the methylation of IC2 is associated with *CDKNC1* and *KCNQ1* expression and *KCNQ1OT1* repression. Methylation and expression follow opposite pattern on the paternal allele. Red circles indicate methylated imprinting centers. Expressed genes are represented as green boxes and silent genes as gray boxes. The orientation of gene transcription is indicated by black arrows

A molecular defect of the 11p15 region can be found in more than 80% of individuals with BWS (Eggermann et al. 2016). Five distinct mechanisms are described:

- Loss of methylation at IC2 locus on the maternal chromosome in 50% of patients
- Gain of methylation at IC1 locus on the maternal chromosome in 5–10% of patients
- Paternal uniparental disomy (UPD) of 11p15 region in 20% of patients
- *CDKN1C* pathogenic mutation on the maternal allele in 5% of sporadic cases and 40% of familial cases
- Chromosomal alterations in 11p15 (duplications, inversions, translocations) in <5% of patients

These alterations are responsible for *IGF2* overexpression (biallelic instead of only paternal expression), which is a key player of adrenocortical tumorigenesis (Gicquel et al. 1997).

Most sporadic cases of BWS are related to somatic mosaicism (Slatter et al. 1994). Especially, UPD arises from postzygotic somatic recombination in early-stage embryos (Henry et al. 1993). Hence the proportion of affected cells is variable from one tissue to another. Molecular testing of blood samples may not be contributive in case of low level of mosaicism in leukocytes. Therefore, testing other tissues—buccal swabs, skin fibroblasts, or if available hyperplastic tumor tissue—can improve the detection rate of mosaic events.

The distinct molecular groups translate into distinct phenotypes. Segmental UPD of 11p15 is commonly associated with high risk of embryonal tumors and lateralized

overgrowth, whereas exomphalos is primarily observed in loss of methylation at IC2 and *CDKN1C* mutations.

9.3.4 Tumor Spectrum, Management, and Prognosis

The prognosis of BWS depends on neonatal period complications and tumor risk.

The morbi-mortality in infants with BWS is mainly due to neonatal complications such as hypoglycemia, major exomphalos, or respiratory obstruction from macroglossia (Smith et al. 2007).

The tumor risk is highest in infants and children under 8 years, whereas adults with BWS do not seem to have an increased risk of tumor development. Embryonal tumors (i.e., Wilms tumor, neuroblastoma, and hepatoblastoma) occur in 8% of children with BWS (Brioude et al. 2013; Mussa et al. 2016). Wilms tumor (also known as nephroblastoma) represents 50% of all tumors, with frequent multifocal and bilateral presentations. Other tumors of the BWS spectrum include hepatoblastoma (15%), neuroblastoma (10%), rhabdomyosarcoma (5%), and ACC (5% of all tumors) (Maas et al. 2016).

The tumor risk and spectrum are strongly related to the genotype. Patients with gain of methylation at IC1 and UPD show the highest risk of tumors, up to 50% (Shuman et al. 2006). Conversely, the tumor risk is only 2–3% in patients with loss of methylation at IC2 (Maas et al. 2016). Patients with gain of methylation at IC1 mostly develop Wilms tumors, whereas patients with *CDKN1C* mutations are rather predisposed to develop other embryonal tumors (Brioude et al. 2013; Maas et al. 2016; Mussa et al. 2016).

Screening using abdominal ultrasound is recommended every 3 months from diagnosis to at least the age of 7 years (Brioude et al. 2013). Treatment strategies and prognosis are the same as in children without BWS. Pediatric tumors are associated with favorable outcomes compared to their adult counterparts, with up to 90% survival in embryonal tumors and 70% in ACC (Porteus et al. 2000; Dehner and Hill 2009).

9.3.5 Risk of Recurrence and Genetic Counseling

The risk of recurrence depends on the underlying molecular defect at the 11p15 region (Cerrato et al. 2008; Baskin et al. 2014). Most cases of BWS are sporadic with a recurrence risk in the family less than 1%. Familial cases account for 15% of BWS and are mostly related to *CDKN1C* mutations, chromosomal alterations in 11p15, and genetic alterations within IC1. These 11p15 alterations are associated with autosomal dominant transmission, with a theoretical 50% risk of inheriting the affected allele. However, the penetrance depends on the sex of the parent from whom the genetic defect is inherited. Thus, the type, size, location, and parental origin of the genetic defect should be taken into consideration for family genetic counseling.

9.4 Li–Fraumeni Syndrome

9.4.1 Definition and Prevalence

Li–Fraumeni syndrome (LFS) is an autosomal dominant tumor predisposition syndrome characterized by a high, various, and early-onset cancer risk (Li and Fraumeni 1969; Li et al. 1988). The diagnosis is commonly made in case of familial clustering of childhood cancers, with ACC, soft-tissue sarcoma, central nervous system tumor, and leukemia as the predominant cancer types. LFS is due to germline pathogenic variants in the *TP53* tumor suppressor gene (Malkin et al. 1990).

LFS has an estimated prevalence of 1 per 20,000 births, although a recent analysis of sequencing databases in unselected patients showed a much higher prevalence of germline pathogenic *TP53* variants than the one estimated from family-based studies (de Andrade et al. 2019). The prevalence of LFS is particularly high in southern Brazil, due to a founder germline TP53 mutation (p.R337H), affecting 0.3% of this population (Pinto et al. 2004; Custódio et al. 2013).

9.4.2 Clinical Diagnosis and Indications of Genetic Testing

After its first description by Li and Fraumeni in 1969 (Li and Fraumeni 1969), several diagnostic criteria have been proposed for LFS. The classical LFS includes a proband with sarcoma at <45 years, a first-degree relative with any cancer at <45 years, and a first- or second-degree relative with any cancer at <45 years or sarcoma at any age (Li et al. 1988). However, this restricted definition does not include some families with tumor associations suggestive of LFS. Therefore, more flexible definitions, characterized as "Li–Fraumeni-like" syndrome, were proposed (Birch et al. 1994; Eeles 1995).

The definition of LFS has evolved after the discovery of its relation to germline *TP53* mutations in 1990 (Malkin et al. 1990). Enlarged diagnostic criteria were then proposed to cover the different clinical presentations associated with these mutations. The last version of diagnostic criteria, known as revised Chompret's criteria, recommends molecular testing in 4 clinical situations (Chompret et al. 2001; Tinat et al. 2009; Bougeard et al. 2015): (1) familial presentation of LFS tumors, (2) multiple primary tumors, (3) rare cancers suggestive of LFS, and (4) breast cancer before the age of 31 years (Table 9.4). These criteria show excellent sensitivity (82–95%) and acceptable specificity (47–58%) (Gonzalez et al. 2009; Tinat et al. 2009). Among patients matching the Chompret's criteria, 30–35% carry a germline *TP53* mutation (Gonzalez et al. 2009; Tinat et al. 2009).

Table 9.4 Revised Chompret's criteria for the genetic testing of Li–Fraumeni syndrome (LFS) (Bougeard et al. 2015)

1. Familial presentation	Proband with tumor belonging to LFS tumor spectrum[a] before the age of 46 years AND at least one first- or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before the age of 56 years or with multiple tumors
2. Multiple primitive tumors	Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before the age of 46 years
3. Rare tumors	Patient with adrenocortical carcinoma, choroid plexus tumor, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history
4. Early-onset breast cancer	Breast cancer before the age of 31 years

[a]*LFS tumor spectrum includes premenopausal breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumor, and adrenocortical carcinoma*

9.4.3 Molecular Diagnosis

LFS is due to germline mutations in the *TP53* tumor suppressor gene. This gene is also the most frequently mutated gene at a somatic level in sporadic cancers. *TP53* gene encodes the p53 protein, a critical transcription factor that promotes cell cycle arrest, DNA repair, and apoptosis in response to stress signals (Reinhardt and Schumacher 2012). Therefore, p53 is frequently referred to as "the guardian of the genome" (Lane 1992).

TP53 alterations in part of LFS are mostly point mutations, with 70% missense and 20% nonsense or splice mutations (Bouaoun et al. 2016). Although distributed all along the gene, some "hotspot" mutations are described. The most common one is the p.R337H Brazilian mutation in exon 10 (Garritano et al. 2010). De novo mutations are frequent, accounting for up to 20% of LFS diagnoses (Renaux-Petel et al. 2018).

Some genotype–phenotype correlations are reported. On the one hand, missense mutations within the DNA-binding domain can exert a dominant-negative effect on the wild-type p53 protein, or even gain an oncogenic function. These mutations are typically associated with a wide range of early-onset cancers and high penetrance (Bougeard et al. 2015). On the other hand, nonsense mutations or gene deletions result in loss of function and are associated with later onset and lower penetrance. Finally, the p.R337H mutation is associated with a limited spectrum and predisposes primarily to ACC and breast cancer (Mastellaro et al. 2017).

9.4.4 Tumor Spectrum, Management, and Prognosis

The lifetime risk of cancer in LFS is very high: 80% of *TP53* mutation carriers will develop at least one malignancy, and 40% will develop multiple malignancies (Bougeard et al. 2015). The median age of first tumor onset of 27 years (Bougeard et al. 2015) and different patterns of cancer are encountered at the different stages of life (Amadou et al. 2018). During childhood, LFS is dominated by the risk of osteosarcoma (30% of *TP53* mutation carriers), ACC (27%), brain tumors (26%, including choroid plexus carcinoma, medulloblastoma, and glioblastoma), soft-tissue sarcoma (23%, mostly rhabdomyosarcoma), and leukemia (9%)(Bougeard et al. 2015). These tumors are otherwise extremely rare in the general population. Early adult life is associated with an increased risk of breast cancer (80%), soft-tissue sarcomas (27%, mostly leiomyosarcoma, liposarcoma, and fibrohistiocytic tumor), osteosarcoma (6%), lung cancer (8%), and colorectal cancer (5%) (Bougeard et al. 2015). LFS patients typically develop these tumors at an earlier age than that observed in sporadic cases. Conversely, the contribution of LFS to tumor development in late adult life seems rather limited. Only 25% of LFS-related cancers occur after the age of 50 years (Amadou et al. 2018). Prostate cancer (7%) is the most frequent tumor at this time (Bougeard et al. 2015).

Childhood ACC is a signature feature of LFS. *TP53* germline mutations have been observed in 50% of children with apparently sporadic ACC in North America and Europe (Wasserman et al. 2015; Bougeard et al. 2015). In Southern Brazil, the founder p.R337H mutation in exon 10 is observed in up to 90% of pediatric ACC cases (Ribeiro et al. 2001). Overall, 3–10% of LFS children will develop ACC at a median age of 2–3 years (Figueiredo et al. 2006; Bougeard et al. 2015). The frequency of *TP53* germline mutations in ACC decreases with age, reaching less than 5% in adults (Herrmann et al. 2012; Raymond et al. 2013a).

In recent years, several surveillance protocols have been proposed to promote early detection of tumors and reduce cancer morbidity and mortality in LFS. The recent consensus from the American Association for Cancer Research recommends that all patients be offered cancer surveillance based on the "Toronto protocol"(Kratz et al. 2017) (Table 9.5). This intensive screening protocol includes annual whole-body, brain, and breast MRI and has proven benefit on early tumor detection and long-term survival (Villani et al. 2011, 2016). Screening for ACC in childhood should start at birth and include complete physical examination, with particular attention to symptoms of precocious puberty and Cushing's syndrome, and abdominal ultrasound every 3–4 months. Biochemical testing for hormone secretion may be performed every 3–4 months, especially in case of inconclusive ultrasound (Kratz et al. 2017).

Finally, the diagnosis of LFS may impact the therapeutic decisions for ACC patients. Since LFS patients are at risk of radio-induced malignancies (Heymann et al. 2010), adjuvant radiotherapy should be avoid for completely resected ACC.

Table 9.5 Modified "Toronto protocol" for the screening of Li–Fraumeni syndrome tumors (Kratz et al. 2017)

Children (birth to the age of 18 years)
General assessment • Complete physical examination every 3–4 months, including blood pressure, growth curve, Cushing appearance, signs of virilization, and full neurologic assessment • Prompt assessment with primary care physician for any medical concerns
ACC • US of abdomen and pelvis every 3–4 months • In case of unsatisfactory US, blood tests may be performed every 3–4 months: Total testosterone, dehydroepiandrosterone sulfate, and androstenedione
Brain tumor • Annual brain MRI (first MRI with contrast; thereafter without contrast if previous MRI normal)
Soft tissue and bone sarcoma • Annual whole-body MRI
Adults
General assessment • Complete physical examination every 6 months • Prompt assessment with primary care physician for any medical concerns
Breast cancer • Breast awareness and clinical breast examination twice a year from the age of 20 years • Annual breast MRI between 20 and 75 years • Consider risk-reducing bilateral mastectomy
Brain tumor •Annual brain MRI
Soft tissue and bone sarcoma • Annual whole-body MRI and US of abdomen and pelvis
Gastrointestinal cancer • Upper endoscopy and colonoscopy every 2–5 years from the age of 25 years
Melanoma • Annual dermatologic examination

9.4.5 Risk of Recurrence and Family Counseling

LFS shows an autosomal dominant inheritance with generally high penetrance. Therefore, all at-risk relatives of an affected LFS patient should be offered genetic counseling.

In Southern Brazil, considering the particularly high incidence of childhood ACC, a genetic neonatal screening for the p.R337H mutation may be proposed (Custódio et al. 2013).

9.5 Other Tumor Predisposition Syndromes

Besides BWS and LFS, responsible for the majority of childhood tumors, ACC was recently described in part of other tumor susceptibility syndromes.

Among those, Lynch syndrome is of particular therapeutic interest. Lynch syndrome is a dominantly inherited tumor predisposition syndrome, due to germline mutations in DNA mismatch repair genes (MMR) *MLH1*, *MSH2*, *MSH6*, and *PMS2*. This syndrome typically confers an increased risk for colorectal, endometrial, small bowel, and upper tract urothelial cancers (Amsterdam Criteria), but also for sebaceous tumors, ovarian and pancreatic cancers, and ACC. Lynch syndrome accounts for up to 5% of ACC cases (Raymond et al. 2013b; Zheng et al. 2016), which is a similar prevalence to that observed in colorectal and endometrial cancers. As for other Lynch syndrome-related cancers, screening for mismatch repair deficiency in tumor tissue using immunohistochemistry and/or microsatellite analysis can orient toward diagnosis. MMR immunohistochemistry shows the absence of nuclear staining (Raymond et al. 2013b). Microsatellite instability can be detected at the genomic level (Bonneville et al. 2017), but classical microsatellite panels used for colorectal cancer screening were found negative in ACC (Raymond et al. 2013b). Finally, the diagnosis of Lynch syndrome impacts treatment strategies. Lynch tumors are hypermutated and present a large number of neoantigens. These features have been associated with response to immune checkpoints inhibitors (Le et al. 2015), which might represent new therapeutic opportunities for Lynch syndrome-associated ACC.

Other tumor predisposition syndromes each account for less than 1% of ACC and include genes classically responsible for endocrine tumors and hyperplasias—such as *MEN1* (Waldmann et al. 2007) or *SDH* genes (Else et al. 2017)—or for non-endocrine tumors—such as *APC* (Gaujoux et al. 2010), *NF1* (Wagner et al. 2005), *MUTYH* (Pilati et al. 2017), or *BRCA2* (El Ghorayeb et al. 2016) germline mutations.

9.6 Conclusions

CNC predisposes primarily to PPNAD, responsible for severe Cushing's syndrome in children and young adults, and more rarely to ACC. Half of childhood ACC occur in part of tumor predisposition syndromes; LFS and BWS should be evoked in first intention in this population. In adults, germline predisposition affects up to 10% of ACC patients, mostly in part of LFS and Lynch syndrome.

Therefore, every patient with newly diagnosed PNNAD or ACC should be considered for genetic counseling, regardless of the family history.

The diagnosis of a tumor susceptibility syndrome in an index case should initiate appropriate screening for other syndrome-related tumors and familial genetic testing.

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