Diagnosis and Management of Hereditary Sarcoma

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Abstract

Sarcomas are rare and heterogeneous diseases that affect a younger population than most epithelial cancers. Epidemiologic studies suggest a strong genetic component to sarcomas, and many familial cancer syndromes have been described, in which sarcomas are a feature. The best known of these are the Li–Fraumeni and retinoblastoma syndromes, study of which has been pivotal to elucidating the molecular basis for the cell response to DNA damage and the cell division. Although much has been learnt about cancer biology from the study of sarcoma families, in general clinical management of increased sarcoma risk has lagged behind other cancer predisposition syndromes. With the advent of genomic tools for genetic testing, it is likely that a substantial fraction of sarcoma patients will be identified as carriers of known risk alleles. The translation of this knowledge into effective risk management programs and cancer treatments will be essential to changes in routine clinical practice.

Keywords

Sarcoma · Genetics · Genomics · TP53

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1 Introduction

Sarcomas are a diverse set of malignancies of the connective tissues, with an estimated incidence of 50–70 per million of the population (Fletcher et al. 2013). Sarcomas are divided pathologically into those arising in soft tissues and those arising in bone. There are in excess of 50 recognised subtypes of sarcomas, which exacerbates problems of accurate classification and underlines the rarity of these conditions. Sarcomas blur into a much more common group of benign connective tissue tumours, and sarcomas not uncommonly arise in pre-existing benign lesions. The strongest known environmental risk factor for sarcomas in general is ionising radiation, with weaker evidence for arsenicals and herbicides (Thomas and Ballinger 2015). Many of the genes implicated in hereditary sarcomas outlined in this chapter play important roles in the cellular response to DNA damage, which has clinical implications for therapy.

Soft-tissue sarcomas are roughly four times more common than bone tumours. The most common subtypes are undifferentiated pleomorphic sarcomas, followed by liposarcomas, leiomyosarcomas and synovial sarcomas. The most common bone tumours are osteosarcoma, Ewing sarcoma and chondrosarcoma. These categories mask a further degree of genetic, histologic and clinical heterogeneity, further complicating the challenges of accurate diagnosis and clinical management. As an era of increasing targeted therapies emerges, the clinical importance of accurate classification is only increasing.

This complexity is also important from a genetic perspective, because in addition to a broad sarcoma susceptibility for genes, such as *TP53*, mutations in other genes are associated with specific sarcoma subtypes. Because sarcomas often arise at a younger age than most epithelial cancers (Fletcher et al. 2013), they likely carry a significant burden of heritable aetiology. Ethnic variation in sarcoma incidence has not been well mapped, again because of their rarity and difficulties in consistent annotation. For example, Ewing sarcoma appears to be more common in Caucasians (Worch et al. 2010), which suggests ethnic modifier influences for a disease which is not associated with recognised familial clustering. Population-based studies suggest a high frequency of multiple primary and secondary cancers in individuals who develop sarcomas (Fernebro et al. 2006; Hemminki and Li 2001).

Sarcoma-associated syndromes have contributed enormously to our understanding of cancer biology, disproportionate to their incidence. Many of these typically autosomal dominant syndromes are described below, although interestingly many of the sarcomas that arise earlier in life, such as Ewing and synovial sarcoma, are not associated with dominant familial patterns. Despite their contribution to biological knowledge, the clinical management of these syndromes has lagged behind breast cancer and bowel cancer. In part, this may be because of the difficulties in risk modification (for example, by early detection and prevention) of cancers that are not only diverse and rare, but are also not limited to an anatomical organ system. Recent advances in genomics as well as imaging technologies may have a significant impact on our ability to identify and modify sarcoma risk. Generating a comparable evidence base for altering clinical practice may be challenging because of their rarity. We summarise what is currently known about hereditary aspects of sarcomas, consider some of the missing information in our knowledge base and conclude by summarising likely future developments in this fast-moving field of research.

2 Hereditary Conditions Predisposing to Sarcoma

2.1 Li–Fraumeni Syndrome

Li and Fraumeni described several families with a high frequency of bone and soft-tissue sarcoma, breast cancer, brain tumours and leukaemia, suggesting a dominantly inherited predisposition (Li et al. 1988; Li and Fraumeni 1969). Known as Li–Fraumeni syndrome (LFS) (OMIM 151623), this constellation of features was subsequently associated with germline mutations in the *TP53* gene (Srivastava et al. 1990; Malkin et al. 1990). Other genes that may phenocopy LFS include *CHEK2* and perhaps *BRCA2* (Bell et al. 1999; Evans et al. 2008). Clinical criteria for defining LFS and identifying candidates for *TP53* testing have evolved (Table 1) (Li et al. 1988; Bougeard et al. 2008; Chompret et al. 2001; Tinat et al. 2009; Bougeard et al. 2015). A broad range of bone and soft-tissue sarcomas account for approximately 25 % of cancers in LFS families, with osteosarcoma, leiomyosarcoma and rhabdomyosarcoma the most common (Ognjanovic et al. 2012). There are some phenotype–genotype correlations. Missense mutations in the *TP53* DNA-binding domain are associated with the earlier age of tumour onset, while frameshift, splice site and nonsense mutations are associated with leiomyosarcoma in older patients (Ognjanovic et al. 2012). *TP53* mutation carriers have an increased lifetime risk of cancer, with estimates traditionally derived from families meeting classical LFS or Chompret criteria (Table 1). In these families, the cancer risk is almost 100 % for females and 73 % for males over a lifetime (Chompret et al. 2000; Wu et al. 2006), with an early age of onset and increased risk of multiple malig-

Table 1 Modification of LFS classification criteria over time

Classification	Year	Criteria
Classic LFS	1988	Proband with a sarcoma diagnosed <45 years of age AND a first degree relative to any cancer <45 years of age AND a first or second degree relative to any cancer <45 years of age OR a sarcoma at any age
Chompret	2001	Proband with a [a]narrow spectrum LFS cancer <36 years of age AND ≥1 first or second degree relative to a narrow spectrum LFS cancer (except breast cancer if the proband has breast cancer) <46 years of age OR multiple primary cancers **OR** Proband with multiple primary cancers, 2 of which are narrow spectrum LFS cancers and the first occurred <36 years of age, regardless of family history **OR** Proband with adrenocortical carcinoma at any age regardless of family history
	2009	Proband with [b]LFS spectrum cancer <46 years of age AND ≥1 first or second degree relative to a LFS spectrum cancer <56 years of age OR with multiple cancers **OR** Proband with multiple cancers (except multiple breast cancers), 2 of which are LFS spectrum cancers and the first occurred <46 years of age **OR** Proband with adrenocortical carcinoma or choroid plexus tumour regardless of family history
	2015	Proband with [c]LFS spectrum cancer <46 years of age AND ≥1 first or second degree relative to a LFS spectrum cancer (except breast cancer if the proband has breast cancer) <56 years of age OR multiple primary cancers **OR** Proband with multiple primary cancers (except multiple breast cancers), 2 of which are LFS spectrum cancers and the first occurred <46 years of age **OR** Proband with adrenocortical carcinoma, choroid plexus tumour or rhabdomyosarcoma of embryonal anaplastic subtype, regardless of family history **OR** Proband with breast cancer <31 years of age

[a]Narrow spectrum LFS cancers include sarcoma, brain tumour, breast cancer and adrenocortical carcinoma

[b]LFS spectrum cancers include soft-tissue sarcoma, osteosarcoma, brain tumour, premenopausal breast cancer, adrenocortical carcinoma, leukaemia and lung bronchoalveolar cancer

[c]LFS spectrum cancers include soft-tissue sarcoma, osteosarcoma, CNS tumour, premenopausal breast cancer and adrenocortical carcinoma

nancies (Gonzalez et al. 2009; Hisada et al. 1998; Mitchell et al. 2013). A reduced cancer risk may occur in individuals not ascertained on LFS criteria, perhaps reflecting unknown modifier influences that increase the penetrance of alleles in familial settings (Mitchell et al. 2013).

Clinical guidelines for surveillance in *TP53* mutation carriers currently centre on breast and bowel cancer preventative measures (CINSW 2015; NCCN 2014; NICE 2013) with little account for sarcomas and other *TP53*-associated malignancies. Research studies have implemented whole-body surveillance utilising various methods including ^{18}Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography (FDG-PET/CT) (Masciari et al. 2008) and whole-body magnetic resonance imaging (MRI; Villani et al. 2011). Although methodologically limited by small sample size and lack of randomisation, screened individuals in the latter study had better clinical outcomes than those who were not screened. A Southern Brazilian study screened neonates for the *TP53* R337H founder mutation and went on to monitor mutation carriers for adrenocortical cancer, one of the commonest malignancies associated with *TP53* seen under 10 years of age (Custodio et al. 2013). Tumours in screened carriers were identified at an earlier stage than those who were not screened. There are several issues to consider in clinical management of TP53 mutation carriers including limiting radiation exposure (Heymann et al. 2010) and the psychological effects and ethical issues associated with potential young age of cancer (Fresneau et al. 2013; Alderfer et al. 2015). Several efforts are underway internationally investigating the many aspects of comprehensive surveillance protocols for *TP53* mutation carriers (Villani et al. 2011; LIFSCREEN 2015; SIGNIFY 2015; ANZCTR 2015; Alderfer et al. 2015; CGP 2015). A surveillance schedule has been proposed to facilitate a consistent international approach while research efforts are ongoing (McBride et al. 2014).

2.2 Gastrointestinal Stromal Tumours (GIST) Predisposition Syndromes

GISTs are a form of soft-tissue sarcoma arising in myenteric cells of Cajal within the gastrointestinal tract, and most commonly affect patients aged 60–65 (Bachet et al. 2013). Most commonly, sporadic may also occur in an autosomally dominant inherited pattern in less than 5 % of cases (Neuhann et al. 2013). The first report of a family displaying characteristics consistent with heritable GIST was made in 1990 (Marshall et al. 1990). In 1998, a gain of function germline mutation in exon 11 of *KIT* was identified in a case of heritable GIST (Nishida et al. 1998). Since then more than 25 kindreds with inherited GIST syndromes (OMIM 606764) have been reported, the majority with *KIT* mutations (Carballo et al. 2005; Robson et al. 2004) reflecting the high frequency (80–85 %) of *KIT* mutations in sporadic GIST (Neuhann et al. 2013). The most common variants are in exon 11 (Nishida et al. 1998; Carballo et al. 2005; Beghini et al. 2001; Maeyama et al. 2001; Adela Avila et al. 2014), but have also been found in exons 8 (Hartmann et al. 2005), 13 (Isozaki et al. 2000; Graham et al. 2007) and 17 (Hirota et al. 1998) of the *KIT* gene. In all reports, an autosomal dominant pattern of inheritance is described with almost 100 % penetrance (Bachet and Emile 2010). GISTs occur most commonly at a young age (40–50 years) often with multiple tumours that are multifocal and arise in the stomach or small intestine (Bachet et al. 2013). In addition to predisposing to GIST,

different germline *KIT* mutations are associated with variable phenotypes, including hyperpigmentation, dysphagia and mastocytosis/urticaria pigmentosa (Neuhann et al. 2013), but consistent phenotype–genotype correlations are still to be determined.

Other genes have been linked to familial GIST. GIST families with germline mutations in *PDGFRA* (exons 12 and 14) (de Raedt et al. 2006; Chompret et al. 2004; Pasini et al. 2007) have also been identified, reflecting the incidence (5–10 %) of somatic *PDGFRA* mutations in GIST (Neuhann et al. 2013). GIST clinical manifestations in germline *PDGFRA* mutation carriers are similar to germline *KIT* mutations with the age at GIST onset in these families being 40–50 years. Other clinical observations in these families are variable but include multiple lipomas and polyps in the small intestine (Pasini et al. 2007), intestinal neurofibromas (de Raedt et al. 2006) and large hands (Chompret et al. 2004).

Approximately, 10 % of gastric GISTs have loss of function in the succinate dehydrogenase (SDH) complex and are KIT/PDGFR wild-type (Miettinen et al. 2013). This is indicated by the loss of SDH subunit B (SDHB) staining by immunohistochemistry and tumours are termed SDH-deficient. These SDH-deficient gastric GISTs typically occur in children and young adults, form multiple tumours and often follow an indolent course (Miettinen and Lasota 2014). Carney triad (OMIM 604287) is a non-familial association of pulmonary chondroma, extra-adrenal paraganglioma and SDH-deficient GIST with a strong female predilection (Carney et al. 1977; Zhang et al. 2010). However, the later-described Carney-Stratakis syndrome (CSS) (OMIM 606864) is characterised by SDH-deficient GIST and paragangliomas and is inherited in an autosomal dominant manner with incomplete penetrance (Carney and Stratakis 2002). Germline mutations in the *SDH* genes *SDHB*, *SDHC* and *SDHD* have been identified in these CSS families (Pasini et al. 2008). More recently, *SDHA* germline mutations have been found in SDH-deficient GIST patients (Miettinen et al. 2013; Miettinen and Lasota 2014; Pantaleo et al. 2011).

There are currently no evidence-based guidelines for risk management of hereditary GIST syndromes. Criteria have been outlined for the identification of potential germline *KIT* and *PDGFRA* mutation carriers and surveillance and treatment recommendations made (Bachet et al. 2013). In clinical management of affected individuals, *KIT/PDGFR* mutant tumours respond well to imatinib, while SDH-deficient and wild-type tumours are less likely to respond as well. Patients with advanced wild-type GIST do not respond to imatinib as well as patients with *KIT* exon 11 mutations (Heinrich et al. 2008).

2.3 Neurofibromatosis Type 1 (NF1)

Neurofibromatosis type 1 (OMIM 162200) previously known as von Recklinghausen's disease (Ferner 2007) is a tumour predisposition syndrome characterised by neurofibromas, café au lait pigmentation, Lisch nodules in the eye, optic

pathway gliomas and bony dysplasia. Cognitive disabilities in children and cardiovascular problems in adults are also associated with this condition (Ferner 2007). NF1 has an incidence of approximately 1 in 3000 individuals (Evans et al. 2010; Huson et al. 1989; Ratner and Miller 2015). A region on chromosome 17 was identified as being associated with NF1 (Barker et al. 1987) and subsequently the *NF1* gene was cloned and identified as a tumour suppressor (Viskochil et al. 1990; Cawthon et al. 1990; Wallace et al. 1990). Germline *NF1* mutations are inherited in an autosomal dominant manner but phenotypic variability provides little evidence for phenotype–genotype correlations (Ratner and Miller 2015). Type 1 neurofibromatosis is diagnosed on clinical criteria with mutation testing generally limited to the prenatal setting (Ferner 2007). In 1988, the National Institutes of Health Consensus Development Conference on Neurofibromatosis set clinical criteria for NF1 (Agaimy et al. 2012).

Germline *NF1* mutation carriers are at increased risk of several malignancies including malignant peripheral nerve sheath tumour (MPNST) (Evans et al. 2002) and GIST (Miettinen et al. 2006) and more rarely juvenile leukaemias (Stiller et al. 1994), phaeochromocytoma (Walther et al. 1999), glomus tumours (Stewart et al. 2010) and rhabdomyosarcoma (Sung et al. 2004; Crucis et al. 2015). MPNSTs contribute significantly to the mortality associated with NF1 (Evans et al. 2011) and there is an 8–13 % lifetime risk (Evans et al. 2002). Individuals with microdeletions in *NF1* have an increased risk of MPNST compared to other *NF1* mutation carriers (De Raedt et al. 2003). The prevalence of GIST in patients with neurofibromatosis has been reported at 7 % (Zoller et al. 1997), but higher rates have been recorded in autopsy studies (Miettinen et al. 2006). Approximately 10 % of duodenal and jejuno-ileal GISTs were associated with *NF1* mutations in a large study at the Armed Forces Institute of Pathology (Miettinen et al. 2006).

There is no evidence that specific surveillance for MPNST or GIST in *NF1* mutation carriers provides benefit. Risk management guidelines have been formulated by several groups and recommendations relevant to sarcoma include annual physical examination, regular monitoring of central nervous system abnormalities and other studies such as MRI only when clinically indicated (Hersh and American Academy of Pediatrics Committee on 2008; Ferner 2007; Ferner et al. 2007). Diagnosing malignant transformation in the setting of NF1 can be fraught as the emergence of lumps is common, and benign tumours often produce symptoms similar to malignancy (Ferner 2007). There is an increased risk of MPNST following radiotherapy (Sharif et al. 2006), and therefore, the use of radiotherapy should be carefully considered. NF1-associated GIST typically occurs in the small intestine as multiple, small asymptomatic lesions (Miettinen and Lasota 2013) with a low mitotic index; however, clinical malignancy is not uncommon (Agaimy et al. 2012). *KIT* and *PDGFRA* mutations are usually not present in these tumours (Miettinen et al. 2006; Kinoshita et al. 2004) and generally respond incompletely to imatinib (Lee et al. 2006; Mussi et al. 2008).

2.4 Other Sarcoma-Associated Hereditary Syndromes

There is insufficient space to do justice to the many genes associated to date with individual sarcoma subtypes, so a brief survey will suffice (Table 2). Osteosarcomas are cancers of osteoblasts and are associated with germline mutations in some well-known tumour suppressor genes. These include the Retinoblastoma gene (*RB1*) and three helicases: *RECQL4* in Rothmund-Thomson (OMIM 268400) and RAPADILINO (OMIM 266280) syndromes; *RECQL3* (*BLM)* in Bloom syndrome (OMIM 210900); and *RECQL2* (*WRN*) in Werner syndrome (OMIM 277700). These are all extremely rare and in each case are associated with clinical features. Mutations in *RB1* are associated with childhood retinoblastoma (OMIM 180200) (Balmer et al. 2006), while Werner syndrome is an autosomal recessive condition associated with progeric features (Sugimoto 2014). Bloom and Rothmund -Thomson syndromes, also autosomal recessive, are characterised by small stature and growth delay, and skin changes (Veith and Mangerich 2015). It should be noted that other malignancies, including other sarcomas, are also reported in these cancer types. Other syndromes linked to increased bone turnover are associated with osteosarcomas, including Paget's disease of bone (OMIM 602080, *TNFRSF11A, SQSTM1, PDB4*) (Ralston and Albagha 2014) and McCune Albright syndrome (OMIM 174800, *GNAS*) (Turan and Bastepe 2015).

Chondrosarcomas, or tumours of cartilage, are associated with a variety of hereditary and congenital genetic conditions. Unlike osteosarcomas, chondrosarcomas arise at an older age and are not chemo- or radio-sensitive. Early detection and surgery is therefore critical to effective treatment. Frequently, syndromic chondrosarcomas arise in the context of pre-existing benign skeletal lesions, such as multiple osteochondromas due to mutations in *EXT1* or *EXT2* (OMIM 133700, 133701) (Musso et al. 2015; Jones et al. 2014; Ciavarella et al. 2013). Ollier's disease and Maffucci syndrome are the best known congenital (but not hereditary) chondrodysplastic conditions that are associated with an increased risk of chondrosarcomas (Verdegaal et al. 2011). They are associated with early-onset chondroid lesions, and in the case of Maffucci syndrome, associated with vascular anomalies, including a predilection for angiosarcomas (Fletcher et al. 2013). The genetic basis for these diseases includes mutations in *IDH1* and *IDH2* (Amary et al. 2011), and *PTHLH* (Collinson et al. 2010). Perivascular epithelioid cell sarcomas (PEComas) are associated with mutations in *TSC1* and *TSC2* and may respond to mTOR inhibitors (Wagner et al. 2010).

Rhabdomyosarcomas are usually childhood cancers arising from skeletal muscle and are associated with a wide range of syndromes, including LFS, basal cell naevus syndrome (also known as Gorlin syndrome) (OMIM 109400). Gorlin syndrome is due to mutations in *PTCH1* and perhaps other members of the Hedgehog signalling pathway including *PTCH2* and *SUFU* (Pastorino et al. 2009; Fan et al. 2008; Johnson et al. 1996) and clinical manifestations include basal cell carcinomas, medulloblastoma and jaw cysts. Rhabdomyosarcoma is also associated with Beckwith-Wiedemann syndrome (OMIM 130650) a disorder of epigenetic origin

Table 2 Genetic syndromes and conditions predisposing to sarcoma

Genomic class	Sarcoma	Syndrome/condition	Gene
Complex	Osteosarcoma	Li–Fraumeni syndrome	*TP53*
		Retinoblastoma	*RB1*
		Bloom syndrome	*RECQL3 (BLM)*
		Familial Paget disease of bone	*TNFRSF11A, SQSTM1*, *PDB4*
		Rothmund-Thomson syndrome	*RECQL4*
		RAPADILINO syndrome	*RECQL4*
		Werner	*RECQL2* (*WRN*)
		McCune Albright syndrome	*GNAS*
	Embryonal rhabdomyosarcoma	Li–Fraumeni syndrome	*TP53*
		Gorlin syndrome	*PTCH1*, *PTCH2*, *SUFU*
		Beckwith-Wiedemann syndrome	*CDKN1C*, *NSD1*, *ICR1*, *H19*, *KCNQ1OT1*
		Neurofibromatosis type 1	*NF1*
		Mosaic variegated aneuploidy	*BUB1B*
		DICER 1 syndrome	*DICER1*
		Costello syndrome	*HRAS*
	Rhabdomyosarcoma (subtype not reported)	Nijmegen Breakage syndrome	*NBS1*
		Li–Fraumeni syndrome	*TP53*
	Leiomyosarcoma/undifferentiated pleomorphic sarcoma	Hereditary leiomyoma and renal cell carcinoma	*FH*
		Neurofibromatosis type 1	*NF1*
	MPNST	Hereditary multiple exostoses	*EXT1*, *EXT2*
	Chondrosarcoma	Retinoblastoma	*RB1*
		Ollier disease[a]	*IDH1*, *IDH2*, *PTHLH*

(continued)

Table 2 (continued)

Genomic class	Sarcoma	Syndrome/condition	Gene
		Maffucci syndrome[a]	*IDH1*, *IDH2*, *PTHLH*
Simple	GIST	Familial GIST	*KIT*, *PDGFRA*
		Carney-Stratakis syndrome	*SDHB*, *SDHC*, *SDHD*
		Neurofibromatosis type 1	*NF1*
	PEComa	Tuberous sclerosis	*TSC1*, *TSC2*
Translocation-associated	Ewing sarcoma	None	
	Myxoid liposarcoma	None	
		None	
	Synovial sarcoma	Retinoblastoma	*RB1*
	Alveolar rhabdomyosarcoma	Costello syndrome	*HRAS*

[a]Not hereditary

involving chromosome 11q15, although the precise genetic basis is not known (Cohen 2005), type-1 neurofibromatosis (Sung et al. 2004; Crucis et al. 2015), Nijmegen breakage syndrome (*NBS*1, a recessive condition associated with short stature and microcephaly and immunodeficiency) (Chrzanowska et al. 2012), mosaic variegated aneuploidy (*BUB1B*, associated with developmental delay and anomalies) (Hanks et al. 2004), DICER1 syndrome (*DICER1*, associated with endocrine phenomena) (Schultz et al. 2014) and Costello syndrome (a congenital myopathy associated with mutations in *HRAS*) (Kratz et al. 2015).

Uterine leiomyosarcomas may be associated with hereditary leiomyomatosis and renal cell carcinoma (HLRCC, OMIM 150800), a cancer predisposition syndrome characterised by cutaneous leiomyomas, multiple benign uterine leiomyomas (fibroids) and early-onset renal tumours with a specific type-II papillary morphology (Schmidt and Linehan 2014; Launonen et al. 2001). Germline mutations in the Fumarate Hydratase (FH) gene are associated with HLRCC (Tomlinson et al. 2002). The estimated lifetime risk of renal cancer is 15 % (Menko et al. 2014). Surveillance recommendations for HLRCC centre around renal cancer risk, but an annual gynaecological review has been suggested as warranted for possible detection of malignancy (Refae et al. 2007). There are reproductive implications for female *FH* mutation carriers to consider also as uterine leiomyomas typically affect young women and may interfere with the ability to bear children.

3 Benign and Intermediate Connective Tissue Tumour Syndromes

It is estimated that there are over 100 benign connective tissue tumours for every sarcoma, and many of these are associated with a hereditary or constitutive genetic basis (Gatta et al. 2011; Myhre-Jensen 1981). In addition to the morbidity due directly to these diseases, the significance of these associations lies in the linkage to both sarcomas and epithelial malignancies. Familial adenomatous polyposis (FAP) should be suspected in individuals presenting with aggressive fibromatosis (AF; also known as desmoid tumour) and is mostly due to germline mutations in the *APC* gene (Fearnhead et al. 2001). This may occur in the absence of a family history, as the de novo rate of APC mutations is estimated at 25 % (Bisgaard et al. 1994). Germline *APC* mutation carriers have a lifetime risk of colorectal cancer nearing 100 % (Burn et al. 1991), and a 12 % risk of AF (Clark and Phillips 1996). Although notionally benign, AF is one of the main causes of death in patients post-colectomy (Sturt and Clark 2006). They are typically non-metastatic but exhibit aggressive local growth patterns, and usually occur in the abdominal wall or mesentery (Lung et al. 2015). Risk management for *APC* mutation carriers focuses primarily on the risk of colorectal cancer but recommendations have included CT or MRI for the detection of AF on an individualised basis (Leoz et al. 2015).

4 Sarcomas not associated with Recognised Syndromes

It is interesting to consider the subset of sarcomas which are not characterised by familial clustering. Many sarcomas are characterised by chromosomal instability (for example, leiomyosarcoma, undifferentiated pleomorphic sarcoma, osteosarcoma), particularly in association with LFS. However, most sarcomas characterised by pathognomonic translocations, such as EWS-FLI1 in Ewing sarcoma (Lessnick and Ladanyi 2012), FUS-CHOP in myxoid liposarcoma (Di Giandomenico et al. 2014) and SYT-SSX in synovial sarcoma (Thway and Fisher 2014), are not associated with known syndromes. This is despite the case that Ewing sarcoma is essentially a paediatric or young adult onset sarcoma, while synovial sarcoma also affects a younger population than most sarcomas. Early age of cancer onset tends to suggest a genetic basis, which makes the absence of reported families a little surprising. Given the historical focus of cancer genetics on dominant cancer families, and single-gene testing based on linkage studies, it is possible that this may be due to non-dominant genetic transmission, or to de novo events that we do not recognise.

5 Future Directions

The traditional focus of cancer genetics on Mendelian dominant families, single-gene testing and breast, bowel and ovarian cancer is going to change over the next decade (Thomas et al. 2015). The driver behind these changes is the impact of genomic tools on mutation identification. The technology ranges from boutique panels comprising a few genes, to whole exome sequencing, and inevitably, whole genome sequencing. A full discussion of this topic is beyond the scope of this chapter. The coming era will see a shift towards ascertainment of risk directly through genetic testing of a broader range of patients than previously. In respect of sarcomas, a recent survey indicated that patients and their families have positive attitudes towards genetic testing for heritable conditions and about genetic research in general (Young et al. 2013).

As these tools are applied to broader populations of cancer patients—and maybe ultimately to the population at large—the architecture of genetic cancer risk will begin to include more quantitative, polygenic elements, as well as the current dominant effects of major cancer genes. It is already clear from studies (predominantly in breast cancer) that common single nucleotide polymorphisms may coincide within individuals with early-onset cancer (Sawyer et al. 2012). However, the effect size attributable to each variant is small, when they overlap their combined effect may be comparable to that seen in individuals carrying known dominant causes of cancer. The key point is that as multiple-gene testing enters the clinic, the ability to discern the effects of multiple variants within an individual will usher in a much more complex era of variant classification. We predict that evidence will accumulate over the next decade of the polygenic contribution to cancer risk at the

population level. Of course, we next need to understand how this information is to be used to help carriers.

Population- or clinic-based ascertainment will also identify the hidden burden of de novo mutations in dominant genes in individuals who lack a classic family history. The precise rates of de novo variation are not known for most genes with certainty, and vary quite significantly from apparently negligible in the case of *BRCA1*, to approximately 20 % in the case of *TP53* (Schneider et al. 2013). For sarcomas, it is possible that a combination of unrecognised de novo and polygenic causes may in part account for the group of early-onset, translocation-associated sarcomas.

Genomic studies are already underway in sarcoma populations to begin the journey of mapping genetic risk. The low-hanging fruit from these studies will come from determining the burden of risk attributable to genes already linked to cancer risk in sarcomas, or for cancers in general. Based on current studies in breast and ovarian cancers (Walsh et al. 2011), even the application of limited gene panels will identify about 15–25 % of sarcoma subjects with known oncogenic germline variation. The clinical importance of these early gene panels cannot be overstated, since utility drives change in medical practice. For some of these genes, we have accepted risk management protocols (e.g. for *APC, BRCA1*). Increasingly, germline genetic variation may also be used to select patients for targeted therapies, such as vismodegib for Gorlin's syndrome (Lopez-Lerma et al. 2015) and poly-ADP ribose polymerase inhibitors for carriers of mutations in *BRCA1* or *BRCA2* (Scott et al. 2015). It is also important to recognise that sarcomas are surgically curable if caught at an early stage. The co-development of technologies such as whole-body magnetic resonance imaging will be important to sarcoma-specific risk management and early-detection programs, as is the case for any multiorgan cancer susceptibility syndrome. Finally, it is likely that knowledge of germline variation in DNA repair genes may directly influence decision-making in the treatment of sarcomas. Radiation is the strongest known environmental risk factor for sarcoma development and also forms a key treatment modality for patients with sarcoma—including in the curative management of these diseases. In the future, the decision whether or not to use radiotherapy may be informed by a more detailed knowledge of carriage of variants impairing normal tissue responses to these treatments.

6 Summary

Sarcomas are rare and heterogeneous malignancies that affect the young. Early age of cancer onset is an important guide to genetic risk. While the study of rare families with excess sarcoma has contributed to fundamental insights into cancer biology, including the *TP53* and cell cycle pathways, a genetic basis for the majority of sarcomas remains to be discovered. Clinically, despite long knowledge of syndromes such as those due to mutations in *TP53,* risk management has lagged behind more common hereditary cancer syndromes such as those associated with

breast and bowel cancer. This is likely because of the multiorgan nature of most sarcoma susceptibility syndromes and because their rarity impedes the generation of an evidence base for effective risk modification. Future developments in genomics, imaging technologies and molecular therapeutics are likely to present opportunities for both ascertainment of the genetic basis for sarcomas, early detection and treatment of affected patients.

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