European Journal of Cancer 92 (2018) 48–53

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Current Perspective

Germline *BAP1*-positive patients: the dilemmas of cancer surveillance and a proposed interdisciplinary consensus monitoring strategy

Phoebe Star [a], Annabel Goodwin [b,c], Rony Kapoor [a,d], R. Max Conway [c,e], Georgina V. Long [a,f], Richard A. Scolyer [a,c,g], Pascale Guitera [a,c,h,*]

[a] *Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia*
[b] *Cancer Genetics, Royal Prince Alfred Hospital, Camperdown, NSW, Australia*
[c] *The University of Sydney, Sydney, Australia*
[d] *The Mater Hospital, Sydney, Australia*
[e] *Ocular Oncology Unit, Save Sight Institute, Australia*
[f] *Royal North Shore Hospital, Sydney, Australia*
[g] *Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia*
[h] *Sydney Melanoma Diagnostic Centre (SMDC), Royal Prince Alfred Hospital, Camperdown, NSW, Australia*

Received 14 December 2017; accepted 21 December 2017

KEYWORDS
BAP1 mutation;
Cancer surveillance;
Screening

Abstract The germline *BAP1* (BRCA1-associated protein-1) mutation and associated cancer pre-disposition syndrome was first described in 2011. Since then, physicians have considered this diagnosis for patients with a characteristic personal or family history of BAP1-associated tumours (mainly uveal and cutaneous melanoma, pleural/peritoneal mesothelioma, renal cell carcinoma and BAP1-deficient melanocytic lesions). However, a positive germline *BAP1* mutation detection creates significant uncertainty in terms of appropriate cancer surveillance. A number of groups have proposed surveillance plans but important management dilemmas remain unresolved. The lifetime risk of developing cancer is not known and it is not clear if surveillance would lead to detecting cancer at an earlier stage or change survival outcomes. A consensus monitoring strategy was initially proposed at the Melanoma Institute Australia Melanoma Multidisciplinary Team meeting and later discussed with specialists in the field of cancer genetics, pathology, radiology, medical oncology, ophthalmology and

* *Corresponding author*: Melanoma Institute Australia, North Sydney, NSW, Australia.
E-mail address: pascale.guitera@melanoma.org.au (P. Guitera).

https://doi.org/10.1016/j.ejca.2017.12.022

dermatology. The objectives were to facilitate early diagnosis, incorporating where possible, clinically based and low/non-ionising radiation imaging modalities, applying the principles of a good screening test and a multidisciplinary focus.

Cancer screening guidelines for patients with a germline *BAP1* (BRCA1-associated protein-1) mutation are not established. It is unclear what an appropriate surveillance plan may entail or even if it will lead to earlier stage at diagnosis or reduce mortality. A consensus monitoring strategy for germline *BAP1* mutation carriers was initially proposed at the Melanoma Institute Australia Melanoma Multidisciplinary Meeting and later discussed with specialists in the field. This discussion was prompted by the need to appropriately manage the next generation of a family with the germline *BAP1* mutation and associated familial cancer syndrome (Pedigree previously published [1]).

In 2011, a novel-inherited cancer predisposition syndrome was proposed in association with the germline *BAP1* mutation [2–4]. Reported carriers have a high incidence of four main malignancies: malignant mesothelioma (pleural and peritoneal, frequency ratio 1:1), uveal melanoma (UM), cutaneous melanoma (CM) and renal cell carcinoma (RCC), as well as a type of *BAP1*-deficient Spitzoid melanocytic tumour. Basal cell carcinomas, breast cancer, cholangiocarcinoma, meningioma, neuroendocrine tumours, and thyroid cancer are also reported in association with the mutation [5]. Cohort studies demonstrate cancer in *BAP1* carriers at higher rates and younger median age of onset compared with the general population (Table 1) [6]. In a review of 76 germline *BAP1* mutation carriers, 53 (69.7%) had developed at least one malignancy and all those without malignancy were under 55 years old [7]. However, the prevalence of this mutation in the general population is unknown and thus the actual cancer risk in *BAP1* carriers could be overestimated.

The *BAP1* gene is a tumour suppressor gene located on chromosome 3 (locus 3p21.1) which encodes the BAP1 protein, a deubiquitinating enzyme. The BAP1 protein is involved in many key cellular functions including DNA repair, deubiquitination of histones, chromatin modulation, transcription regulation and cell cycle regulation [8]. Germline *BAP1* mutations are inherited in an autosomal-dominant pattern. Each somatic cell of the affected individual carries one mutant and one wild-type *BAP*1 allele. To lose *BAP1* tumour suppressor function in a cell, the normal wild-type allele must acquire a somatic mutation. Significant mutations are those that affect either the nuclear localisation sequence, resulting in retention of the protein in the cytoplasm, or the N-terminal ubiquitin carboxyl hydrolase catalytic domain, affecting deubiquitinating activity [9].

One of the clinical hallmarks of the germline *BAP1* mutation is a distinct type of melanocytic nevus, estimated to occur in 75% of patients [10] and first described by Thomas Wiesner *et al.* [2]. Lesions typically present as skin-coloured, pink or tan dome shaped or pedunculated papules, on the scalp, trunk and limbs from the second decade of life and may range from 5 to 50 in number [2]. This entity is referred to variously as Wiesner's nevus, melanocytic *BAP1* mutant atypical intradermal tumours, nevoid melanoma-like melanocytic proliferations and 'BAP-oma'. In the upcoming 4th edition of the World Health Organisation (WHO) Classification of Skin Tumours, the terms *BAP1*-inactivated nevus and *BAP1*-inactivated melanocytoma (the latter being used for cases with atypical features) are used. Pathologically they have been grouped under the umbrella term of atypical Spitz tumours due to overlapping histological features between Spitz nevi and spitzoid melanoma, but it is now clear that they have no particular relationship to Spitz nevi and are now classified separately. A key difference between these tumours and classic Spitz nevi is their molecular profile, as they lack expression of *BAP1* on immunohistochemistry and usually are BRAFV600E mutant [9]. Depending on the degree of atypia, they may be classified as *BAP1*-inactivated melanocytomas of uncertain malignant potential, however, in our experience, cases displaying typical morphological features with loss of BAP1 protein expression have benign clinical behaviour and should be classified as *BAP1*-inactivated nevi [9]. Nevertheless, in practice, they should be monitored closely and excised if their appearance changes [9].

The diagnosis of a *BAP1*-inactivated melanocytic nevus or melanocytoma, in the presence of a personal or family history of cancer, should prompt referral to a cancer genetic service for counselling and possible genetic testing. In a cohort of 174 patients with the germline *BAP1* mutation, Rai *et al.* found that in 75% (130/174) of those diagnosed with one of the four main malignancies or *BAP1*-deficient melanocytic tumours, 90% (117/130) had a family history of at least two of these main tumours in a first- or second-degree relative [6]. The mutation status of these affected relatives is often unknown. Other cohort studies show that patients with the *BAP1* mutation are more likely to have a history of CMM and UM rather UM alone [7,8,11,12]. The frequency of the