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Mini-review

Cutaneous melanoma susceptibility and progression genes

Femke A. de Snoo[a], Nicholas K. Hayward[b,*]

[a]Department of Human and Clinical Genetics, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
[b]Queensland Institute of Medical Research, 300 Herston Rd, Herston, Qld 4029, Australia

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Abstract

This review aims to provide an up-to-date view on our understanding of the molecular genetics of melanoma development. It gives an overview of genes (and loci) currently known to be substantially involved in melanoma predisposition and progression. Broadly, the review falls into 3 sections: genes/loci involved in melanoma susceptibility through germline mutation, tumor suppressor genes somatically mutated or deleted in melanoma, and oncogenes mutated somatically in melanoma. The main cellular pathways in which these genes are involved are summarized and discussed. From this it is evident that abberations of cell cycle regulation, DNA repair and receptor-mediated signal transduction are important for melanocytic neoplasia.

Keywords: Melanoma; Mutation; Predisposition; Progression; Oncogene; Tumor suppressor

1. Preamble

The purpose of this review is to discuss genes that have been found to play a substantive role in the development of cutaneous melanoma, such as those that confer a highly significant predisposition to melanoma if mutated in the germline, or, contribute to the development of melanoma when they are mutated or deleted somatically. For the sake of brevity, and to limit the scope somewhat, this review will not consider 'low risk' or 'modifier' predisposition genes. For information on these genes the reader is referred to other recent reviews that cover this topic e.g. [1]. Thus all loci discussed in this article are by the authors' definition at least, 'moderate to high risk' melanoma genes. The catalog of mutated genes in melanoma has then been used to determine the cellular pathways of most importance for development of this neoplasm—pathways in which other components represent likely candidates for a role in melanomagenesis.

Abbreviations APC, adenomatosis polyposis coli; BCC, basal cell carcinoma; CS, Cockayne syndrome; LFS, Li-Fraumeni syndrome; LFL, Li-Fraumeni-like syndrome; LMM, lentigo maligna melanoma; LOH, loss of heterozygosity; MEN 1, multiple endocrine neoplasia type 1; MAPK, mitogen-activated protein kinase; NER, nucleotide excision repair; NM, nodular melanoma; OM, ocular melanoma; PJS, Peutz-Jeghers syndrome; RR, relative risk; SCC, squamous cell carcinoma; SSM, superficial spreading melanoma; TTD, trichothiodystrophy; UVR, ultraviolet radiation; WRN, Werner syndrome; XP, xeroderma pigmentosum.

* Corresponding author. Tel.: +61 7 3362 0306; fax: +61 7 3845 3508.
E-mail addresses: desnoo@lumc.nl (F.A. de Snoo), nickh@qimr.edu.au (N.K. Hayward).

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2. Introduction

The incidence of melanoma is rising rapidly in most fair-skinned populations, currently varying between 7 (Western Europe) to >50 (Queensland, Australia) cases per 100,000 per annum [2,3]. Although there is evidence of stabilizing incidence figures in Australia, possibly due to education on limiting sun exposure and the substantial increase in public knowledge concerning melanoma over the past decades, mortality figures have not declined.

Across several population-based studies 1–13% of melanoma cases reported the occurrence of melanoma in at least one first-degree relative [4]. Hence it is commonly accepted that melanoma predisposition is hereditary in ~10% of all cases. But even in high sun exposure areas such as Queensland, Australia, less than 5% of melanoma probands report two or more first- or second-degree relatives affected with melanoma [5].

Susceptibility in some melanoma families with large numbers of cases is consistent with autosomal dominant inheritance of a single major gene. However, this does not appear to account for the bulk of familial clustering of melanoma, since segregation analysis in a large population-based sample of families failed to show a single gene being responsible for melanoma transmission [6]. Thus the majority of familial melanoma may be due to a polygenic mode of inheritance.

If a characterized germline mutation is not present there are no clear cut criteria for 'familial melanoma', but as a working definition clinicians and researchers generally use this term to describe families in which there are at least 3 cases of melanoma. However, in low sunlight areas such as northern Europe, 'familial melanoma' is often defined when melanoma occurs in as few as 2 first-degree relatives. Additionally, individuals in whom multiple melanomas occur in the absence of a family history of the disease are of concern, since many of these cases have been found to harbour mutations in CDKN2A (reviewed in [7]). As illustrated below, clinical suspicion of a hereditary component to melanoma predisposition should be considered when pancreatic cancer, uveal melanoma or nervous system tumors occur in close relatives of melanoma cases.

Several linkage analyses and candidate gene searches have been performed in familial melanoma. Melanoma predisposition has also been assessed in the context of germline mutations of genes underlying a number of other syndromes. These studies have been summarized in the following four sub-sections.

3. Familial melanoma susceptibility genes

3.1. CDKN2A [OMIM#600160; location: 9p21]

Involvement of a 9p locus in melanoma development was first indicated by cytogenetically detectable loss or translocation of this region in melanomas [8]. Subsequent loss of heterozygosity (LOH) studies [9] indicated the existence of a tumor suppressor gene, which was supported by germline loss of this region in a person with multiple primary melanomas [10]. Lod scores over 10 were obtained by linkage analysis in families in which melanoma was considered the sole phenotype, rather than including a nevus phenotype as well [11]. This finding was confirmed by several groups [12–15] and led to the cloning and identification, from the 9p21 region, of the first melanoma susceptibility gene [16]. This melanoma predisposition gene has been known by several different names: MTS1, INK4A, and CDKN2, but the currently accepted gene nomenclature is CDKN2A, which stands for *c*yclin-*d*ependent *k*inase *in*hibitor *2A*.

By using different first exons, 1α and 1β respectively, CDKN2A encodes two unrelated proteins, p16INK4A (commonly referred to as p16) and p14ARF (*a*lternative *r*eading *f*rame). Both proteins are tumor suppressors involved in cell cycle regulation. P16INK4A negatively regulates cell growth by arresting cells at G1; p14ARF enhances apoptosis and blocks oncogenic transformation. They act via the two critical pathways important in cell cycle control: the Rb and p53 pathways. P16INK4A negatively affects cell division via inhibition of CDK4 and CDK6. Inhibition of these kinases prevents phosphorylation of pRb, keeping it active as a repressor of E2F-mediated gene transcription and preventing cell cycle entry. P14ARF in turn, blocks HDM2 induced degradation of p53 [17,18] (Fig. 1).

Most germline mutations in CDKN2A are missense mutations found in exons 1α and exon 2, some of which are recurrent. Where analysed, all but one (due to replication slippage) of the recurring mutations within