Published in final edited form as:

Cancer Prev Res (Phila). 2018 March ; 11(3): 121–124. doi:10.1158/1940-6207.CAPR-17-0255.

Marshalling the translational potential of *MC1R* for precision risk assessment of melanoma

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Abstract

Melanoma rates have been increasing in the United States, and neither primary (sun protection and avoidance) nor secondary (skin examination) prevention is practiced consistently, even by those with melanoma risk factors. Inherited variation at *MC1R* is a robust marker for increased risk of melanoma, even among individuals with “sun-resistant” phenotypes. Although *MC1R* conveys important information about inherited melanoma risk for a broad spectrum of individuals, concerns that *MC1R* feedback could have negative consequences, including increased distress about melanoma, inappropriate use of health services, and development of a false sense of security are valid and require empirical examination. The time is right for high quality research focusing on the translation of *MC1R* genotype into clinical and public health practice. If studies show *MC1R* genetic risk screening is effective at motivating behavior change, more melanomas may be detected at earliest stages for which surgical excision is highly curative or a large number of melanomas may be prevented altogether. While other genetic markers for melanoma susceptibility may emerge in the coming years, the burgeoning research agenda on the public health translational potential of *MC1R* genetic risk screening will inform and usefully advance current and future precision risk assessment of melanoma.

Introduction

The incidence of melanoma has tripled in the last four decades, and the rising prominence of this potentially fatal skin cancer in younger adults is particularly alarming (1, 2). Most melanomas are caused by ultraviolet radiation (UVR), predominately due to sun exposure, and with recent contributions from exposure to artificial UVR sources (3). Primary prevention efforts for melanoma seek to mitigate the development of disease through the reduction of daily UVR exposure through use of hats and clothing to block sun exposure, and use of sunscreen (4). Limiting UVR exposure has the potential to reduce melanoma rates by at least 65% (5).

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Disclosure of Potential Conflicts of Interest

The authors declare no potential conflicts of interest

Secondary prevention for melanoma focuses on the early detection of melanocytic lesions by means of thorough skin screening examinations conducted either by a trained professional or completed carefully and routinely at home (6). Although public health messaging promoting sun protection and skin awareness has been available for years, only 35% of the United States population uses sunscreen consistently, and only 20% of Americans report having had a total- body skin examination (7–10). Poor prevention behaviors also extend to Hispanics, an important and growing segment of the American population (11). Over the past decade, researchers have considered the communication of genetic test results as a potential means to motivate behavior change in the general population. For melanoma, information on inherited variation in the melanocortin-1 receptor (*MC1R*) gene may be one risk screening tool that could shape physician- patient communication to motivate melanoma primary and secondary prevention behaviors. The characteristics of *MC1R*, with non-trivial increased risk of melanoma in persons inheriting specific variants, the high prevalence of variant carriers in the population, and the relevance of carrier status to individuals at low phenotypic risk of disease, make it an ideal genetic marker for feedback to general population subgroups to relay information about heightened disease risk.

The time is right for high quality research focusing on the translation of *MC1R* genotype into clinical and public health practice.

The promise of *MC1R* as a genetic risk screening tool

MC1R encodes a protein central to pathways that signal the production of melanins. It exhibits impressive genetic variability, with the majority (61%) of individuals of European ancestry carrying as least one non-synonymous variant that has potential to affect native *MC1R* function (12). In contrast, most *MC1R* variants related to African ancestry are synonymous changes with little if any potential to impact native *MC1R* function (13, 14). The nine most prevalent variants at *MC1R* range in frequency from about 0.5% to 11% in the general population, and the inheritance of one of these variants is a robust marker for increased risk of melanoma (12). This finding is consistently observed across varied populations of European ancestry, including persons identifying as Hispanic and of Mediterranean descent (15, 16).

These *MC1R* variants impart a 1.5- to 2.7-fold increased odds of melanoma (12), which are comparable in strength to several other melanoma risk factors including family history of disease and phenotypic characteristics, although disease odds associated with common or atypical moles are stronger and range upward to 10-fold (17, 18) Importantly, even among individuals with “sun-resistant” phenotypes, including those with darker hair color, fewer freckles, darker skin tones, and/or a proclivity to tan, *MC1R* risk variants show robust associations with risk of melanoma (12). Thus, *MC1R* genotype conveys information about inherited risk of melanoma for a broad spectrum of individuals, including those with darker pigmentary phenotypes who may be unaware of their personal susceptibility to melanoma.

Attributable risk refers to the amount of disease reduction possible through the “removal” of a particular exposure. The amount of melanoma risk attributable to the carriage of one of the nine most prevalent *MC1R* variants ranges from 1.2% to 8.9%, and the attributable risk

summed across the nine variants reaches 40% (Table 1, (12). Thus, at least theoretically, if knowledge of *MC1R* genotype is salient to patients, the potential to impact prevention behaviors across a large portion of the general population is quite possible.

Ongoing research investigating *MC1R* as a genetic risk screening tool

Genetic testing for *MC1R* could lead to heightened, more precise, and more personalized feedback regarding melanoma risk that is persuasive and motivational, in line with well-established health behavior theories (e.g., The Health Belief Model, The Theory of Planned Behavior, (19). Concerns regarding the potential that *MC1R* feedback will increase distress and worry about melanoma, result in over- or inappropriate use of health services, or lead to a false sense of security about melanoma in those found not to be at increased risk will need to be examined empirically, despite the fact that these concerns have not been borne out in other contexts where SNP feedback has been provided (20). It also may be that the low level of risk (~2 to 3-fold) associated with *MC1R* variant carriage may not provide a potential motivational impetus for behavior change.

There are several ongoing research studies striving to obtain empirical evidence to inform whether *MC1R* genotyping can be incorporated into clinical and/or public health practice to impact melanoma risk prevention behaviors. Three intervention studies use randomized designs to test the efficacy of feedback of genetic information. One study set in Australia provides risk information based on a panel of 42 SNP markers in 21 genomic regions known to be associated with melanoma risk that includes eight risk variants in *MC1R*. A pilot phase assessed behavior changes three months post-intervention and found promising results in the mean number of standard erythemal doses (a measure of overall UVR dose) comparing the control arm receiving only non-genetic information about melanoma prevention and early detection to the intervention arm receiving information on personalized genomic risk along with non-genetic information (21). Two additional studies, one set in Florida and one in New Mexico (22) are assessing feedback of risk information based on carriage of *MC1R* genotype alone. Findings from these three studies, all designed to assess behavior changes out to one year post-intervention, are expected over the next several years. Of note, the two ongoing studies in the United States have incorporated a core content of shared risk feedback materials, including Spanish translations (23), and there is a healthy cross-fertilization of idea and practice experience across the investigators of all three ongoing studies.

Planning for dissemination of *MC1R* genetic results to the public

Testing and feedback for high penetrance melanoma genetic risk (e.g. genetic testing for rare mutations in the cyclin dependent kinase inhibitor 2A [*CDKN2A*] gene with members of melanoma families) requires intensive pre- and post-test education and counseling conducted by a certified genetic counselor. In contrast, *MC1R* genetic risk screening and feedback to members of the general population will need alternative methods of testing and provision of feedback.

Given that risk levels associated with carriage of high risk *MCIR* variants are comparable to other melanoma risk factors commonly discussed in behavioral interventions and standard clinical practice such as family history, it can be argued that feedback of *MCIR* genotype should not require formal genetic counseling *per se*. Furthermore, the resource demands of in-person genetic counseling coupled with the limited number of certified genetic counselors reduce the feasibility of this implementation method in community-based clinics and other public health contexts relevant to the general population. The determination and communication of *MCIR* risk status has potential to improve melanoma prevention efforts given that genetic risk information is novel, may lead to fruitful discussions with physicians and family, and may help individuals understand how genetics and environment together help to inform their skin cancer risk, all potentially leading to risk appreciation and potential behavior change. Additionally, in the future *MCIR* may be able to be combined with other known melanoma risk factors in order to provide individuals with more precise risk levels than are currently available.

Dissemination strategies for *MCIR* genotype results could include receipt of information via web-based interface or postal mail or via telephone call with a trained (non-genetic counselor) public health professional. In a study offering *MCIR* testing as part of a multiplex panel of markers for other diseases, participants were receptive to receiving genetic results in the mail followed by a phone call with a trained research educator; while the services of a trained genetic counselor were made available, none of the study participants selected this option (24). Studies are underway that will confirm the comprehensibility and acceptability of these approaches to *MCIR* test information and feedback (22). Another option is to have *MCIR* results delivered directly to primary or dermatological health care providers, which will allow for ongoing patient-physician communication focused on skin cancer prevention informed by *MCIR* status. Regardless of communication channel and whether individuals receive feedback that they have higher risk, average risk, or no *MCIR* variants, the fundamental goal is to ensure clarity of recommendations regarding primary and secondary prevention behaviors. Ideally, feedback of *MCIR* genotype will maximize motivation for protection in those at highest risk, and avoid undermining prevention behaviors in those at lower risk for *MCIR*, who may indeed have other risk factors for melanoma or who should be reminded of population recommendations for sun protection (4). Although confirmation of efficacy for interventions incorporating precision risk assessment needs to precede dissemination and implementation efforts, the rapidly evolving field of public health genomics and its intersection with skin cancer warrants ongoing discussions regarding these important next steps. Further, the current development of scalable precision risk assessment interventions that reach broad segments of the population will facilitate and speed dissemination and implementation in the coming years.

Next steps and future directions

In the coming years, precision risk assessment of melanoma may well include genetic risk screening such as *MCIR* testing. Genetic information may well provide highly salient information that may raise the immediacy of primary and secondary prevention behaviors in those at heightened risk. However, in other behavioral domains such as diet, physical

activity, smoking cessation, and alcohol use, genetic risk feedback does not consistently increase health behavior change (25). For many individuals, genetic risk feedback for melanoma likely requires targeting of other important health behavior change mechanisms such as increasing confidence in performing consistent sun protection, or increasing perceived control over health (26). Many of the existing genetic risk feedback studies oversample research volunteers who were already highly motivated to change their behavior at baseline, even before receiving genetic risk feedback (27), so it is a high priority to examine the impact of *MC1R* testing in individuals with a range of attitudes towards genetic testing and melanoma risk behavior change. Further, specific subgroups such as those who engage in intentional tanning, either indoor or outdoor, or diverse populations including Hispanics may be particularly likely to benefit, given their relative lack of awareness about skin cancer and melanoma (28). If studies show that *MC1R* genetic risk screening proves to be effective for motivating behavior change, a significant proportion of melanomas may be detected at its earliest stage for which surgical excision is highly curative or a large number of melanomas may be prevented altogether. While other genetic markers for melanoma susceptibility relevant in the general population may certainly emerge in the coming years, the burgeoning research agenda on the public health translational potential of *MC1R* genetic risk screening will inform and usefully advance current and future precision risk assessment of melanoma.

Acknowledgments

Grant Support

This work was supported, in part, by grant awards from the American Cancer Society to PAK (RSG-14-162-01-CPPHS) and the National Institutes of Health to JLH (R01 CA181241).

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Table 1

Allele frequency and population attributable risk for melanoma for the nine most prevalent *MC1R* variants ^a

<i>MC1R</i> variant	Allele frequency (%)	Attributable risk % (95% confidence interval)
V60L	10.6	8.2 (3.7 – 11.8)
D84E	0.4	1.2 (0.6 – 1.5)
V92M	7.0	4.7 (3.1 – 6.1)
R142H	0.6	1.5 (0.7 – 2.0)
R151C	5.7	8.9 (7.1 – 10.3)
I155T	0.8	1.2 (0.4 – 1.7)
R160W	7.2	8.3 (6.7 – 9.6)
R163Q	4.7	2.7 (1.2 – 3.8)
D294H	1.3	3.3 (2.7 – 3.8)

^a All estimates are abstracted from *Pasquali et al.* and are derived from a pooled analysis of over 5100 melanoma cases and 12,100 controls aggregated from 17 international studies (12).