

BRAF-mutant Melanoma: Another Angle in the Genetics of Skin Cancer

Research suggests that BRAF mutations in the presence of particular MC1R variants influences melanoma susceptibility.

By Jonathan Wolfe, MD

The CDKN2A germline mutation has been linked to melanoma and, as discussed last month, researchers have made progress in assessing the relative risk associated with this germline mutation. Another known mutation associated with melanoma is the BRAF mutation. Despite some historic disagreement about the association between BRAF mutations and melanoma susceptibility, recent evidence confirms a correlation and suggests it may be linked to expression of MC1R, the gene encoding the melanocortin-1 receptor.¹

MC1R

Landi, et al. in 2005 reported findings regarding MC1R based on an Italian cohort.² An investigation involving 267 melanoma patients and 382 controls sought to identify the prognostic value of identified MC1R variants or Agouti Signaling Protein (ASIP) gene polymorphisms in relationship to sporadic and familial melanoma risk, melanoma thickness, and disease progression.

Carrying MC1R variant alleles increased the risk of familial or sporadic melanoma by two to four times compared with carriers of wild-type MC1R. Interestingly, this association was stronger in individuals with fewer additional risk factors, such as dark skin or few nevi. Carriers of variant alleles were also three- to four-times more likely to

have thick melanomas. The ASIP polymorphism, however, was not associated with melanoma risk, pigmentation, or nevi.

Another study involving a cohort of 100 sporadic cutaneous melanoma patients and 100 unrelated controls from central Italy supports that MC1R variants are indicators of melanoma risk.³ Sequence analysis of the coding region of the MC1R gene uncovered a total of 26 MC1R variants. Of note, carriers of particular high-penetrance alleles that define MC1R variants strongly associated

with the red hair color phenotype (R variant, associated with non-expression of MC1R) had an increased risk of melanoma. Stratifying for clinical and UV exposure risk factors significantly increased the melanoma risk associated with the high-penetrance allele, mainly in the presence of atypical nevi, more than 50 melanocytic nevi, high recreational sun exposure, and occupational sun exposure.

BRAF

Like MC1R variants, BRAF mutations have largely been associated with

New In Your Practice

Breathing In Psoriasis. The smoke may be beginning to clear when it comes to the link between psoriasis and smoking. According to the results of a prospective analysis reported in the November issue of the American Journal of Medicine, current and past smoking and cumulative measures of smoking are linked to incidence of psoriasis in women. Researchers examined 887 women with psoriasis over a 14-year period. Compared with women who had never smoked, current smokers had a multivariate relative risk for psoriasis of 1.78. For past smokers, relative risk was 1.37.

No Kidding. Although the majority of acne cases occur in adolescents and teenagers, a new study confirms that a significant portion of adults have acne well beyond the teenage years. Researchers surveyed a random sample of men and women aged 20 and older to determine the prevalence of both persistent acne that continued after adolescence and new adult-onset acne. While the vast majority of participants responded that they had acne at one time or another, usually in their teenage years, results suggest that for every age group following the teenage group, the incidence of acne was significantly higher among women than men.

Doubly A-peeling. The new Kinerase Pro+Therapy In-Office Peel System (Valeant) exfoliates the skin via a two-part preparatory product and in-office peel. The In-Office Peel exfoliates dead skin cells and stimulates epidermal cell turnover Valeant says. The Pro+Therapy Procedure Recover SPF 30 helps infuse moisture back into the skin and allow for a more accelerated healing time, the company says.

melanoma risk, though the nature of the relationship has been unclear. Now research suggests that BRAF mutations in the presence of specific MC1R variants may indicate melanoma susceptibility.

In a 2006 publication¹ involving 85 samples from their earlier Italian cohort² and a new American cohort (n=112), Landi et al observed that BRAF oncogene mutations are evident in the majority of melanomas identified on skin that has little to no evidence of chronic sun-induced damage (CSD). By contrast, such mutations are less frequent in melanomas found on skin with evidence of chronic sun-induced damage. Based on these findings, the team suspected a susceptibility factor must influence development of BRAF mutant melanoma. They turned their attention to MC1R.

Non-CSD melanomas occurred in younger patients and arose more frequently on intermittently-exposed anatomic sites, such as the trunk. BRAF mutations were more common in non-CSD melanomas with MC1R mutations compared to those with wild-type MC1R alleles.

The team first classified patients in two groups: those with homozygous MC1R wild-type and all others. BRAF mutations occurred six to 13 times more often among those with at least one MC1R variant allele. Subclassification of MC1R status according to zero, one, or two variant alleles showed that the odds ratio for non-CSD melanomas increased progressively. MC1R variation did not affect the frequency of BRAF mutations in CSD melanomas, though the researchers note the number of BRAF-mutant CSD melanomas was too low to permit formal statistical analysis.

Stratifying tumors based on presence or absence of BRAF mutations, the odds ratio for development of non-CSD melanoma climbed from

7.2 for individuals with one MC1R variant allele to 17 for those with multiple variant alleles. BRAF mutations were present in more than 80 percent of non-CSD melanomas in individuals with two variant MC1R alleles and about 30 percent of individuals with wild-type MC1R. BRAF mutations were not associated with phenotypic characteristics usually associated with sun sensitivity.

Because melanomas on mucosal-lined body cavities, the soles, palms, and subungual sites have low BRAF mutation frequencies compared to a roughly 60 percent mutation frequency in non-CSD melanoma, the team concludes that sun exposure is necessary for development of BRAF mutations. Yet, the relatively low incidence of BRAF-mutant melanoma in older patients with evidence of CSD suggests no simple link between sun exposure and BRAF-mutant melanomas. Landi et al conclude that variant MC1R alleles are "at least one component" of melanoma susceptibility related to BRAF mutations.

A subsequent study indicated that BRAF mutations contribute to benign melanocytic hyperplasia but also suggested that they contribute to invasive melanoma only in conjunction with other mutations.⁴ This past spring, researchers showed that BRAF mutations (or NRAS mutations, which were also studied) were more likely in patients with more than 14 black nevi compared with patients with up to four black nevi.⁵ UV exposure is once again implicated: BRAF mutations were more likely in individuals with high exposure to ambient UV radiation between zero and 20 years of age.

The Lone Detractor

One study has failed to identify a role for BRAF mutations in influencing melanoma susceptibility.⁶ That study identified only three BRAF germline mutations in four of 569 malignant

melanoma patients. The estimated rate of BRAF germline mutations in a sample of 358 consecutively selected patient samples was only 0.29 percent. Nonetheless, the preponderance of data suggests that the presence of BRAF mutations indicates melanoma susceptibility, particularly among individuals with MC1R variant alleles.

It appears that the presence of MC1R variants may independently influence melanoma susceptibility, but the presence of these variants in conjunction with BRAF mutation indicates a specific risk. Because BRAF-mutant melanomas may occur at an earlier age, on skin that typically does not receive excessive sun exposure, and tend to be thick, knowledge of an individual's BRAF status may allow appropriate monitoring and early intervention. This may suggest an avenue for patient screening in the future. Given suggestions that UV exposure plays a role in tumorigenesis even among genetically predisposed patients, sun avoidance and protection strategies remain important. ☐

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