MC1R Called Useful Flag for Melanoma Risk

BY BRUCE JANCIN

DENVER — Identification of individuals possessing certain melanocortin-1 receptor gene variants may aid in detection of those at increased risk of melanoma.

New evidence indicates the melanoma risk associated with melanocortin-1 receptor (MC1R) high-risk variants is strongest in individuals who would be classified as lower risk by the classic phenotypic criteria such as darker hair, skin, and eye color and absence of freckles, Peter A. Kanetsky, Ph.D., reported at the annual meeting of the American Association for Cancer Research.

"What these data are showing us is that, for certain people, genotype does mean something. If you have red hair we know you're at increased risk for melanoma, and knowledge of MC1R really isn't going to tell us a lot; however, for somebody who has dark hair, knowing MC1R might give us a clue as to who is going to be at increased risk," explained Dr. Kanetsky, an epidemiologist at the University of Pennsylvania, Philadelphia.

In the past decade MC1R has emerged as a potent marker of melanoma risk. What is now clear, however, is that the increased risk associated with inheritance of high-risk MC1R variants is fortuitously stronger in, and perhaps confined to, individuals with protective phenotypes such as darker complexion and absence of freckles, he continued.

Dr. Kanetsky presented a case-control study involving 779 melanoma patients and 325 controls, all with complete MC1R genotyping.

Possession of a high-risk MC1R variant was associated with an overall 1.9-fold increased risk of melanoma. Upon closer inspection, though, the risk was essentially confined to individuals who wouldn't usually be thought to be at increased risk because they possessed protective phenotypes.

Among individuals with moderate or heavy freckling, a high-risk MC1R variant didn't confer any additional increase in melanoma risk beyond that associated with a low-risk MC1R genotype, but in subjects with mild freckling, a high-risk MC1R variant was associated with a 2.5-fold increase in risk compared with a low-risk genotype. In those with no freckling, a high-risk MC1R variant brought an eightfold increase in risk.

Similarly, a high-risk MC1R variant didn't increase melanoma risk in individuals with red or blond hair, but in those with dark hair it boosted the risk 2.4-fold. And again, subjects with 11 or more sunburns prior to age 18 years had no further increase in melanoma risk if they possessed a high-risk MC1R variant, while a high-risk variant conferred a 2.6-fold increase in risk among individuals with one to three sunburns prior to age 18 and a 3.7-fold increased risk in those with no sunburns before age 18.

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DR. KANETSKY

In contrast, the risk of melanoma associated with high-risk MC1R variants was greatest in those with a total nevus count of 54 or more or with 4 or more dysplastic nevi, both known to be strong markers of increased melanoma risk.

To confirm their findings, he and his coinvestigators turned to the published literature. They found seven studies on melanoma risk stratified by MC1R associations, which they compiled in a meta-analysis. As in their own study, the meta-analysis showed that the risk associated with inheritance of a high-risk MC1R variant was largely confined to individuals with darker hair, eyes, and skin color or with a high nevus count.

Based upon his study findings, Dr. Kanetsky estimated that 8%-33% of all melanomas could be detected at an early stage and potentially cured by screening for high-risk MC1R variants in patients with protective phenotypes. ■

Melanoma Risk Factors Appear to Vary by Age

BY RENÉE MATTHEWS

Environmental factors, such as smoking and severe sunburn, were more important than genetic factors in establishing risk for melanoma in older patients, according to the findings of an observational case-control study.

The study also found that melanoma risk factors in older patients (aged 60 and older) were different than those already established for a younger population. Other risk factors cited included prolonged occupational sun exposure, blond or red hair, and a personal (but not family) history of nonmelanoma skin cancer, noncutaneous neoplasia, or melanocytic nevi.

"The most striking differences in melanoma incidence and mortality occur in the elderly," wrote Dr. Eduardo Nagore of the department of dermatology at the Instituto Valenciano de Oncología, Valenica, Spain, and his colleagues. In the United States, for example, the melanoma mortality rate in older patients increased 157% from 1969 to 1999, with a nearly fivefold increase in incidence in older men.

Thicker melanomas were found to be associated with aging—bearing in mind that Breslow thickness is the most accurate prognostic tool in cutaneous melanoma; lentigo malignant melanomas and acral lentiginous melanomas are more prevalent in this age group; and aging itself, independent of Breslow thickness, ulceration, and node metastases, is an independent prognostic factor.

For the current study, the investigators selected consecutive melanoma patients who visited the institute in Valenica for the first time or for a control visit. To be included, they had to be aged 60 years or older and have a diagnosis of melanoma that had been histopathologically confirmed.

The final sample after deaths and loss to follow-up was 160 patients (54% men, median age 68 years). There were 318 controls—two age- and sex-matched controls for each melanoma case, except for one, a 96-year-old man (J. Eur. Acad. Dermatol. Venereol. 2009 June 26 [doi:10.1111/j.1468-3083.2009.03353.x]).

The data for both cases and controls were derived from an interview and a physical examination by two dermatologists. Details of the following were obtained: intermittent sun exposure, such as during sunbathing or sports; occupational sun exposure—chronic exposure from an outdoor job such as gardening, farming, or sailing—and the duration in years; the lifetime number of episodes of severe and light sunburns; smoking history; personal history of noncutaneous neoplasias and nonmelanoma skin cancer; family history; phototype; and hair and eye color. In the physical examination, the investigators recorded the number of melanocytic nevi of more than 2 mm in diameter and the presence of solar lentigines and actinic keratoses.

The results of univariate comparisons between the cases and the controls showed that a higher proportion of melanoma patients had blue or green eyes, blond or red hair and a low phototype, and a history of sunburns. A higher percentage of melanoma patients also reported having had many years of occupational sun exposure and having smoked, and there was a higher prevalence of solar lentigines, actinic keratoses, and melanocytic nevi, and of a personal history of nonmelanoma skin cancer and other noncancerous neoplasias, the authors reported. However, not all of these factors showed significance in multivariate analyses.

"Chronic sun exposure and smoking seem to be a risk factor of developing melanoma in the elderly in contrast to the entire population," wrote the authors, who also put the number of lifetime severe sunburns in this category. "On the other hand, broadly demonstrated melanoma risk factors such as low phototype, fair eye color, and family history of melanoma have not shown significance in patients [aged 60 or older]."

None of the authors disclosed any conflicts of interest. ■

Demise of Accutane Won't Affect Access to Isotretinoin

BY ALICIA AULT

Citing a significant loss of market share, Roche announced in June that it will cease manufacturing the retinoid Accutane, but dermatologists say that the company's pullout will not affect patients' access to the drug and will not have any impact on the risk management program known as iPledge.

The move does not reflect isotretinoin's safety or efficacy, said Dr. Stephen P. Stone, chairman of the American Academy of Dermatology's task force on retinoids. It appears that " this decision was financial and did not have anything to do with the perceived safety of the drug or the perceived willingness of dermatologists to use the drug," said Dr. Stone in an interview.

In a statement, Roche noted that generic competitors now own the market for prescription isotretinoin. Accutane has less than a 5% share for the acne therapy, said the company.

The company "has been faced with high costs from personal injury lawsuits that the company continues to defend vigorously," according to Roche.

Accutane was first marketed in 1982; the initial round of suits mostly alleged the drug was associated with a potential for depression and suicide. More recently, at least 500 suits have been filed alleging that Accutane causes irritable bowel disease.

The generic companies aren't likely to skirt future litigation, said Dr. Stone, a past AAD president and professor at Southern Illinois University School of Medicine in Carbondale.

A spokeswoman for one of the generic manufacturers, Barr Laboratories Inc., said that Barr intended to continue making and distributing isotretinoin.

Dr. Neil S. Goldberg, a dermatologist in Bronxville, N.Y., said in an interview that he agreed that plaintiffs' suits were likely to continue. But, he said, isotretinoin "is still a miracle drug" for acne and that he would not expect dermatologists to suddenly stop using it. He had already switched to using generic forms, partly because insurers made it less attractive for patients to use the brand, but also because he views them as largely equivalent, he said.

Dr. Stone, on the other hand, said he believed that iPledge had been responsive to dermatologists' complaints. He disclosed that he is on the scientific advisory board for iPledge. ■