Several Cancer Susceptibility Variants Also Affect Melanoma Risk

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Pleiotropy refers to a single genetic locus having multiple phenotypic effects. Evidence of pleiotropy can suggest shared molecular mechanisms or disease susceptibility pathways between phenotypes. Several regions of the genome demonstrate pleiotropic effects with multiple cancers, but the extent of these pleiotropic relationships has not been fully characterized. To identify pleiotropic genetic variants that may impact melanoma risk, Drs. Jonathan Kocarnik and Ulrike Peters and colleagues in the Public Health Sciences Division evaluated a panel of genetic variants previously associated with other cancers for an association with melanoma. As recently reported in *PLoS One*, the authors provided confirmatory evidence of such an association for two variants, while also providing additional suggestive evidence for a third variant that may have a male-specific effect.

Melanoma is the most serious form of skin cancer. While the largest risk factor for melanoma is ultraviolet radiation exposure, several genetic variants have also been found to impact risk. Many of these variants are expected to affect melanoma risk through their impact on pigmentation. By looking for pleiotropic associations with genetic variants associated with other cancers, additional mechanisms of melanoma susceptibility may be identified.

As such, the authors evaluated 181 single nucleotide polymorphisms (SNPs) associated with various cancers for an additional association with melanoma. For each SNP, the authors performed meta-analyses across five studies, totaling over 2,000 melanoma cases and 20,000 controls. Three of these studies were participants in the Population Architecture using Genomics and Epidemiology (PAGE) study, while the other two were collaborating cohort studies of health professionals.

From these analyses, the authors found two SNPs associated with melanoma after correction for multiple comparisons. These variants are located in the *TERT/CLPTM1L* locus, a well-known pleiotropic region that has been associated with several cancers, including melanoma and lung cancer. Similar to previous findings, these variants previously associated with an increased risk of lung cancer were also found to be associated with a decreased risk of melanoma. "These pleiotropic effects in opposite directions are interesting not only from the standpoint of elucidating

tumor biology," said lead author Dr. Kocarnik, "but also from a risk interpretation and communication standpoint." Whereas most genetic variants are generally thought of as only impacting risk for one phenotype or only increasing or decreasing risk, pleiotropic variants such as these will require a more nuanced understanding and discussion.

Because previous melanoma studies have shown sex differences in anatomical location, risk of metastases, and survival, the authors also performed analyses stratified by sex. One additional variant, a prostate cancer SNP between *TPCN2* and *MYEOV*, showed a suggestive association with melanoma in males but not in females. While not reaching statistical significance after multiple comparisons adjustment, several lines of evidence offer biological plausibility for the finding. Two coding variants in the ion channel gene *TPCN2* have been associated with hair pigmentation, while *MYEOV* is an oncogene that includes variants implicated for multiple cancers.

The authors had previously reported a sex difference in the association with melanoma for another SNP in a solute-carrier gene associated with pigmentation. Other studies have demonstrated the functional importance of ion and small molecule transport to melanogenesis and the pigmentation pathway, and that these processes can be up or down regulated by sex hormones. "Together with our sex-specific findings, these lines of evidence raise questions regarding potential sex differences in the relationships between ion transport, pigmentation, and melanoma risk," said Dr. Kocarnik. "It is possible that sex differences in circulating levels of these hormones impact ion exchange or tyrosinase activity in a way that modifies the effect of these variants on melanoma risk, perhaps through alterations to melanogenesis or skin pigmentation." Future research will be needed to further explore these potential relationships.

Other Public Health Sciences Division researchers contributing to this project were Drs. Chris Carlson and Charles Kooperberg.

Kocarnik JM, Park SL, Han J, Dumitrescu L, Cheng I, Wilkens LR, Schumacher FR, Kolonel L, Carlson CS, Crawford DC, Goodloe RJ, Dilks HH, Baker P, Richardson D, Matise TC, Ambite JL, Song F, Qureshi AA, Zhang M, Duggan D, Hutter C, Hindorff L, Bush WS, Kooperberg C, Le Marchand L, Peters U. 2015. Pleiotropic and Sex-Specific Effects of Cancer GWAS SNPs on Melanoma Risk in the Population Architecture Using Genomics and Epidemiology (PAGE) Study. *PLoS One*. 10(3):e0120491.

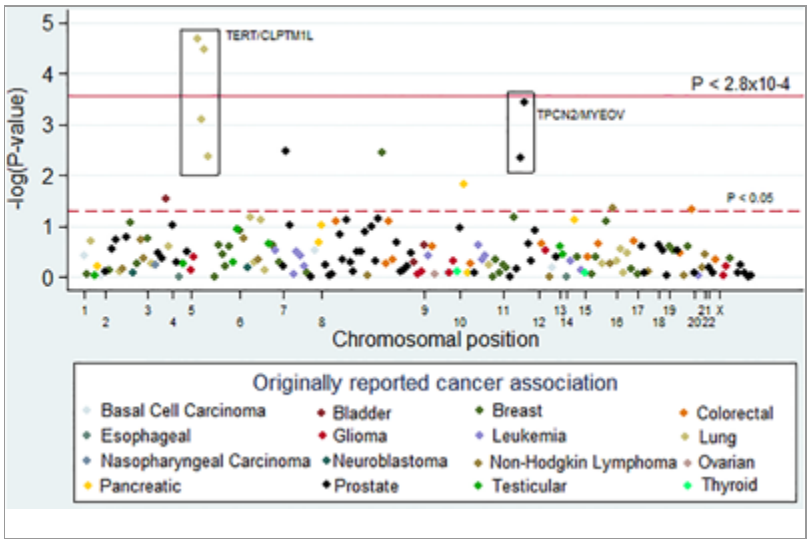

Image from the publication.

This pleiotropy-colored Manhattan plot shows the –log(10) p-value for the association between melanoma and SNPs previously associated with other cancers. The solid line denotes the Bonferroni-corrected significance threshold for this analysis (0.05/181 SNPs).