

NEW INSIGHTS INTO MELANOMA BIOLOGY, PATHOGENESIS, AND EPIDEMIOLOGY

Role of X-chromosome in pathogenesis

Melanoma survival rates are superior for women versus men around the world. Although this was once believed to be due to earlier detection or involvement of different sites in women, more recent research suggests the explanation lies elsewhere,¹ and there is no evidence for a hormonal influence on melanoma survival. **Alan Spatz**, of McGill University in Montreal, Quebec, examined whether the X chromosome inactivation machinery in women can explain (at least in part) the differences between the sexes for melanoma outcomes. As Dr. Spatz explained, if an oncogenic mutation affects an X-chromosome gene, it will always promote tumorigenesis in males, as it will be expressed on the single copy of the X chromosome in males. However, if the mutation involves the inactivated X chromosome in females (and it does not escape inactivation), then woman will be spared the tumorigenic impact of the mutation.² Similarly, an inactivating mutation of a tumor-suppressor gene on the X-chromosome will lead to tumorigenesis in males, but not females, if the mutation only occurs on the inactivated X chromosome.

Dr. Spatz described the results from a study using array comparative genomic hybridization to evaluate DNA and RNA extracted from 48 primary melanomas (32 females, 16 males) and compare with rates of distant metastasis-free survival (DMFS) ≤ 3 years or follow-up > 3 years. Among the 32 females, losses in the X chromosome were significantly associated with DMFS ($P=.009$), and the affected X chromosome was always the inactive X chromosome (9/9). Among the 16 males, losses in the Y chromosome were significantly associated with DMFS ($P=.015$). This is consistent with the notion that the Y chromosome is a mirror of the genes escaping inactivation of the X chromosome. Further analyses identified *PPP2R3B* (or *PR48*) as a gene that is located on the X chromosome in females (Xp22), escapes inactivation of the X chromosome, and is located on the Y chromosome in males (Yp11). Analyses showed *PPP2R3B* expression was significantly associated with DMFS (multivariate $P=.0007$). *PPP2R3B* is a serine/threonine protein phosphatase 2A regulatory subunit that mediates the dephosphorylation of CDC6 by PP2A and controls initiation of DNA replication in humans. Overexpression of CDC6, a replication licensing factor, promotes assembly of the prereplication complex.

Dr. Spatz concluded that these studies show a specific pattern of X and Y chromosome losses associated with melanoma progression, and that *PPP2R3B* appears to be an important tumor suppressor gene whose loss is associated with tumor progression. Differential expression of *PPP2R3B* may contribute to the gender effect on melanoma survival.

References

1. de Vries E., Nijsten TE, VisSuperior survival of females among 10,538 Dutch melanoma patients is independent of Breslow thickness, histologic type and tser O, et al. *umor site. Ann Oncol.* 2008;19:583-589.
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The GenoMEL report

Nelleke Gruis, of Leiden University Medical Center in Leiden, The Netherlands, described recent results from the Melanoma Genetics Consortium (GenoMEL) pointing to some key players in melanoma predisposition. GenoMEL is an international research consortium encompassing more than 20 participant centers from across the globe, and coordinated by the University of Leeds in the United Kingdom. The mission of GenoMEL is to identify melanoma susceptibility genes, assess the impact of variations in these susceptibility genes on risk of melanoma and other cancers, and evaluate gene-environment interactions.

Recently, a genome wide association pooling study (GWAS) involving 1,598 cutaneous melanoma cases and 2,465 controls throughout Europe and Australia was performed in an attempt to identify melanoma susceptibility genes, and particularly lower penetrance genes. High penetrance genes such as *CDKN2A* were located several years ago; susceptibility genes remaining to be identified are likely to be lower penetrance and more difficult to find. The cases in GWAS were genetically enriched (ie, cases were selected for early-onset melanoma, multiple primary melanoma, or family history). Initial genotyping and quality control analyses are now complete, Dr. Gruis said at the meeting, and although the data are still being analyzed, they point to a locus of interest on chromosome 20q11.22. A GWAS using pooled DNA of solely Australian melanoma cases highlighted the potential significance of this region for increased melanoma risk.¹ In particular, 2 single-nucleotide polymorphism (SNP) variants of the locus were highly associated with melanoma (combined $P < 1 \times 10^{-15}$), with a per allele odds ratio (OR) of 1.75.

Dr. Gruis noted that the *ASIP* (encoding agouti signaling protein) gene is located within the 20q region of interest, and that *ASIP* is associated with other known risk factors for melanoma such as skin sensitivity to sun, freckling, and red and blonde hair. Moreover, another recent study of 2,121 European individuals with cutaneous melanoma, 2,163 with basal cell carcinoma (BCC), and more than 40,000 controls, showed an *ASIP* variant conferred significant risk of melanoma (OR, 1.45; $P = 1.2 \times 10^{-9}$) and BCC (OR, 1.35; $P = 1.2 \times 10^{-6}$).² Similarly a variant of the *TYR* (encoding tyrosinase) pigmentation gene significantly increased risk of melanoma (OR, 1.21; $P = 2.8 \times 10^{-7}$) and BCC (OR, 1.14; $P = 6.1 \times 10^{-4}$), and an eye color variant in *TYRP1* (encoding tyrosinase related protein) increased risk of melanoma (OR, 1.15; $P = 4.3 \times 10^{-4}$). Furthermore, the pigmentation genes were associated with melanoma even after adjustment for effect of pigmentation. Also, the increased risk associated with each particular gene appears small, melanoma is a polygenic trait, so the combined effects may be substantial.

References

1. Brown KM, Macgregor S, Montgomery GW, et al. Common sequence variants on 20q11.22 confer melanoma susceptibility. *Nat Genet.* 2008;40:838-840.
2. Gudbjartsson DF, Sulem P, Stacey SN, et al. *ASIP* and *TYR* pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. *Nat Genet.* 2008;40:886-891.