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Towards the use of precision medicine in predicting cutaneous squamous cell carcinoma risk among solid organ transplant recipients

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Wei and colleagues report findings combining data from two observational cohorts of solid organ transplant recipients (OTRs) at different medical centres showing that *OCA2/HERC2* locus variants impact the time to first cutaneous squamous cell carcinoma (cSCC) post-transplant.¹ OTRs with two blue-eye-associated alleles for *OCA2/HERC2*, variants rs916977 and rs12913832, each had an estimated median time to first cSCC of 14.2 years post-transplant, which was 12.3 and 7.4 years earlier, respectively, compared with OTRs with two corresponding brown-eye-associated alleles. The impact on cSCC risk appears dependent on the genetic alleles themselves rather than the particular phenotype as self-reported blue eye colour did not confer similar cSCC risk. Their findings suggest that among OTRs, *OCA2/HERC2* variants could serve as a novel biomarker for identification of individuals at risk for early-onset cSCC.

OCA2 and *HERC2* are major genes that interact to determine skin pigmentation and eye colour. *OCA2* encodes a P protein involved in tyrosine transport, a crucial process for the production of melanin, whereas a conserved regulatory element in the *HERC2* gene modulates *OCA2* expression in the human iris and functions as the main genetic determinant of eye colour. The *OCA2/HERC2* rs916977 and rs12913832 single-nucleotide polymorphisms (SNPs) are attractive genetic variants for risk of early cSCC as they have been strongly linked with low pigmentation capacity.^{2,3} Low melanin production increases the vulnerability of DNA in keratinocytes to ultraviolet radiation-induced damage that can spur cellular transformation to cSCC. This increased vulnerability to DNA damage is especially pertinent for OTRs, whose long-term immunosuppression can further promote carcinogenesis.^{4,5}

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Conflicts of interest

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There are few studies that assess how allelic variants influence genetic susceptibility to cSCC in transplant populations. Although this study focused on only two SNPs that had previously been associated with skin cancer risk, these findings are of great interest and should stimulate exploration of other cSCC risk loci implicated in population-based genome-wide association studies (GWAS),^{6,7} and system-based approaches examining structural variants to better elucidate genes driving cSCC pathogenesis in OTRs. A whole-genome approach could help identify common biological pathways for discovered structural variants. Furthermore, examining associations between cSCC risk and imputed gene expression levels in GWAS can also help identify candidate causal genes and identify novel genes for further study. Current studies in this field have thus far focused on common variants, including minor allele frequencies > 15% as in this study, but future investigations testing rarer variants might uncover more risk loci to further delineate underlying oncogenic pathways in cSCC.^{6,8,9}

Although this is a preliminary study, Wei *et al.*¹ demonstrate that risk prediction models can be extended to incorporate a transplant patient's genetic susceptibility to cSCC to better identify individuals at higher risk of early cSCC development post-transplant and tailor screening intensity. This personalized strategy could improve on and ultimately even replace risk stratification based on conventional phenotypic risk factors, which are currently used to guide dermatological screening and evaluations. Thus, augmenting risk-prediction models with genomic risks can pave the way for precision medicine, and provide new opportunities to translate genetic information to early clinical interventions and ultimately improve clinical outcomes.

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