Exploring genetic evidence for sex-dependent risk factors for melanoma

G J M Shanika R Jayasinghe[1,2], Lee E Wheless[3], Rebecca I Hartman[4], Mathias Seviiri[1,2,5], Stuart MacGregor[1,2], Matthew H. Law[1,2,5]
[1]Statistical Genetics, Population Health, QIMR Berghofer, Brisbane QLD, Australia
[2]School of Biomedical Sciences, Faculty of Health, Medicine and Behavioural Sciences, the University of Queensland, Brisbane, QLD, Australia
[3]Tennessee Valley Healthcare System VA Medical Centre, Nashville, TN, USA
[4]Dermatology Section, VA Boston Healthcare System, Boston, Massachusetts, USA
[5]School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia

Background
Melanoma incidence shows significant variability between men and women, particularly across different anatomical sites within fair-skinned populations. However, the extent to which genetic and phenotypic risk factors interact differently between men and women across body sites is not yet fully understood. Furthermore, previous studies stratified by sex or body sites often suffer from limited sample sizes, which restricts the ability to draw conclusive insights.

Methods
We used the int2MR method to identify if melanoma risk factors exhibited sex-biased effects on melanoma overall and by body sites. Int2MR, an integrative Mendelian randomisation (MR) method, integrates group-specific and combined genome-wide association study (GWAS) summary statistics to detect group-specific exposure interaction effects.
Genetic instruments for melanoma risk factors (exposures) were derived from large-scale GWASs, including pigmentation traits (Million Veteran Program (MVP)), nevus count, and tanning response (QSkin), using linkage disequilibrium clumping. We used sex-specific and body-site-specific melanoma GWASs from a previously published study as IV-to-outcome. Finally, the largest melanoma GWAS meta-analysis conducted to date will be integrated as the group-combined GWASs.

Results
Using only group-stratified melanoma GWAS for int2MR, we found no significant interaction between sex and any of the assessed risk factors for melanoma risk ($p >$ FDR threshold of 0.05 for all traits; e.g. Nevus×sex; 95% CI = (-1.182 - 0.602)). Skin colour (ordered from very fair to brown) showed a body-site-biased (head and neck (reference group) vs lower limbs) significant effect on melanoma (Skin colour× body-site; beta = 0.377, se = 0.13, p = 0.004), indicating fairer skin increases melanoma risk more on the head and neck than the lower limbs.

Conclusions
Our findings show that fair skin increases melanoma risk more at chronically sun-exposed sites, indicating a body-site-specific effect of skin colour on melanoma risk driven by UV exposure. Next, we will integrate group-combined GWASs for int2MR analysis, which will enhance the power for detecting melanoma risk factors with sex or body-site interaction effects. The findings of this approach will provide a comprehensive exploration of sex or site-specific interactions with melanoma risk factors. Identifying any such differences may inform targeted intervention strategies to improve therapeutic outcomes for both men and women.