MHC-II genotypes are independent predictors of anti-PD1 immunotherapy response in melanoma.

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Background

- Immune checkpoint blockade (ICB) therapies have shown remarkable success in the treatment of cancer, but their efficacy varies widely among patients.
- Tumour mutation burden (TMB) and total neoantigen load are regarded as the most accurate genomic biomarkers, yet outcomes remain hard to predict.
- ICB responses are mediated through the presentation of neoantigens by the highly polymorphic Major Histocompatibility Complex (MHC).
- Neoantigen prediction accuracies are extremely low (Claeys et al., Cancer Research, 2023).
- We hypothesize the MHC genotype could be an essential determinant of treatment outcomes.

1: Direct association studies with MHC genotypes are unfeasible

2: MHC genotypes are independent predictors of ICB response

3: Observed survival effect depends on prior anti-CTLA4 treatment

4: MHC genotypes lead to enrichment of cancer hallmark gene sets

Conclusion

- The MHC genotype, quantified using a simple metric, has potential as a new genomic biomarker for ICB response in melanoma.
- The MHC class II genotype is associated with responses to sequential anti-CTLA4 and anti-PD1 treatment.
- Obtaining the MHC genotype is non-invasive (only requires a blood sample). It can be determined using common sequencing technologies (WGS, WES and RNA-Seq).
- Our proposed biomarker is static and not influenced by prior mutational selection or immunoeediting.
- Further validation of our biomarker in larger clinical datasets and across different cancer types is required.