

Dissecting neoantigen drivers of immunotherapy response in Merkel Cell Carcinoma

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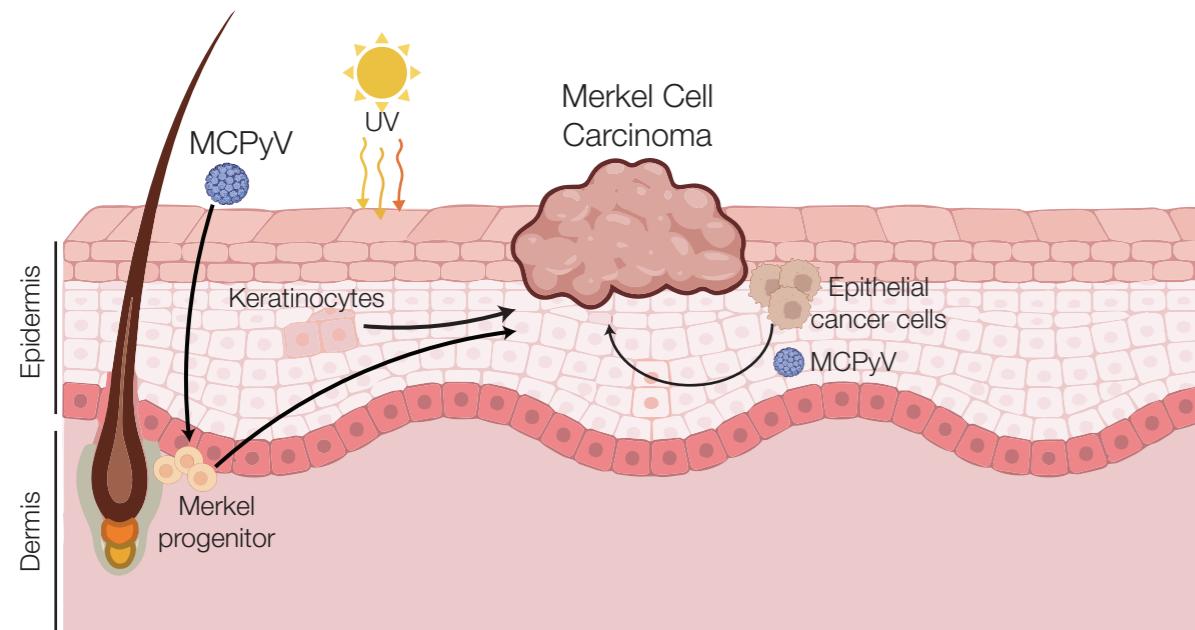
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→ Higher mutational rate
→ Lower mutational rate

The etiology of Merkel Cell Carcinoma could be caused by UV exposure or by the integration and replication of the Merkel Cell Polyoma Virus (MCPyV)¹.

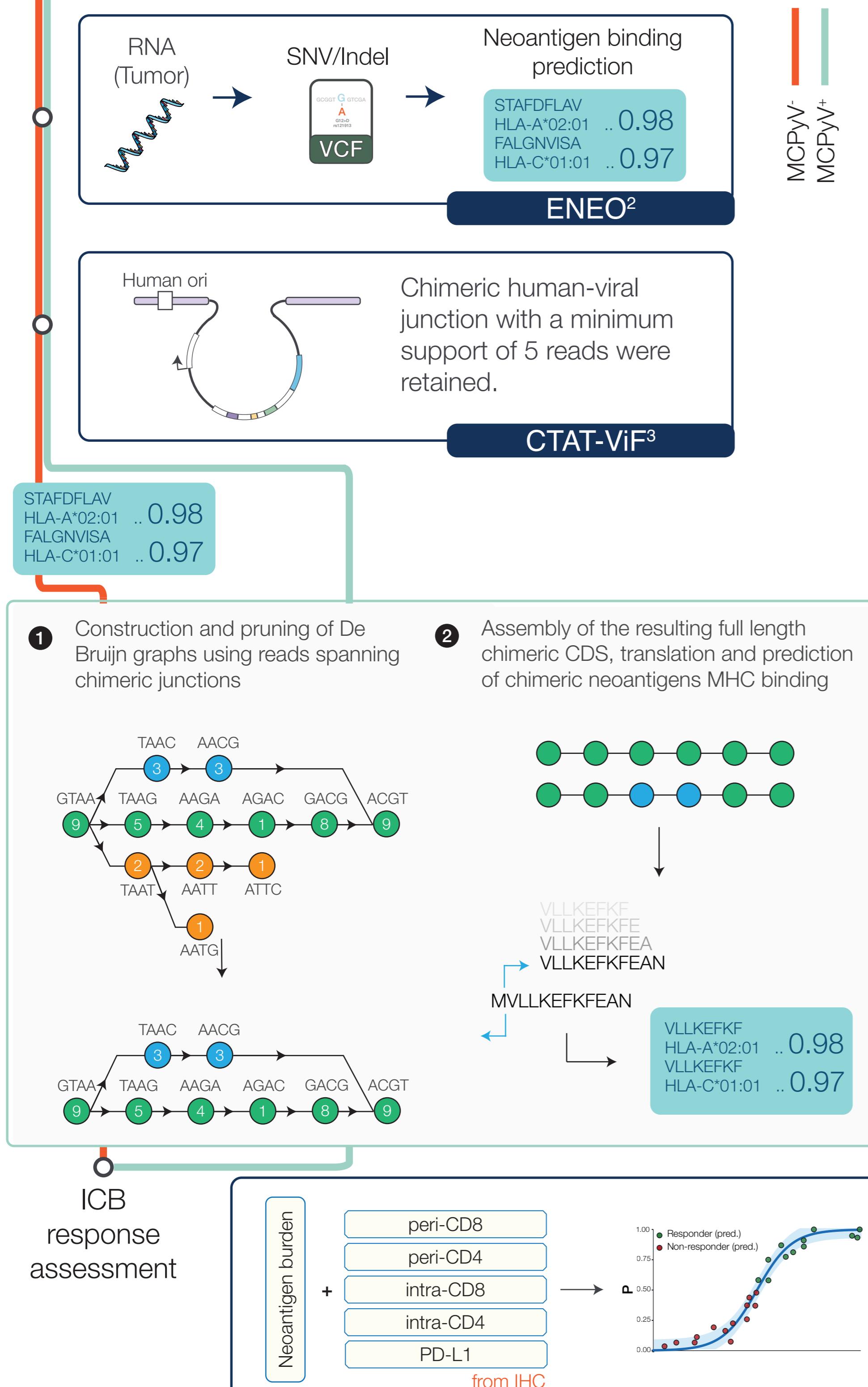
Immunotherapy with immune checkpoint inhibitors (ICB) is the first line therapy for **MCC patients**, for both MCPyV⁺ and MCPyV⁻ cases.

However **no dedicated approaches for neoantigens profiling in MCC exists**, leading to a scarce understanding of the prognostic factors of successfully response to ICB therapy.

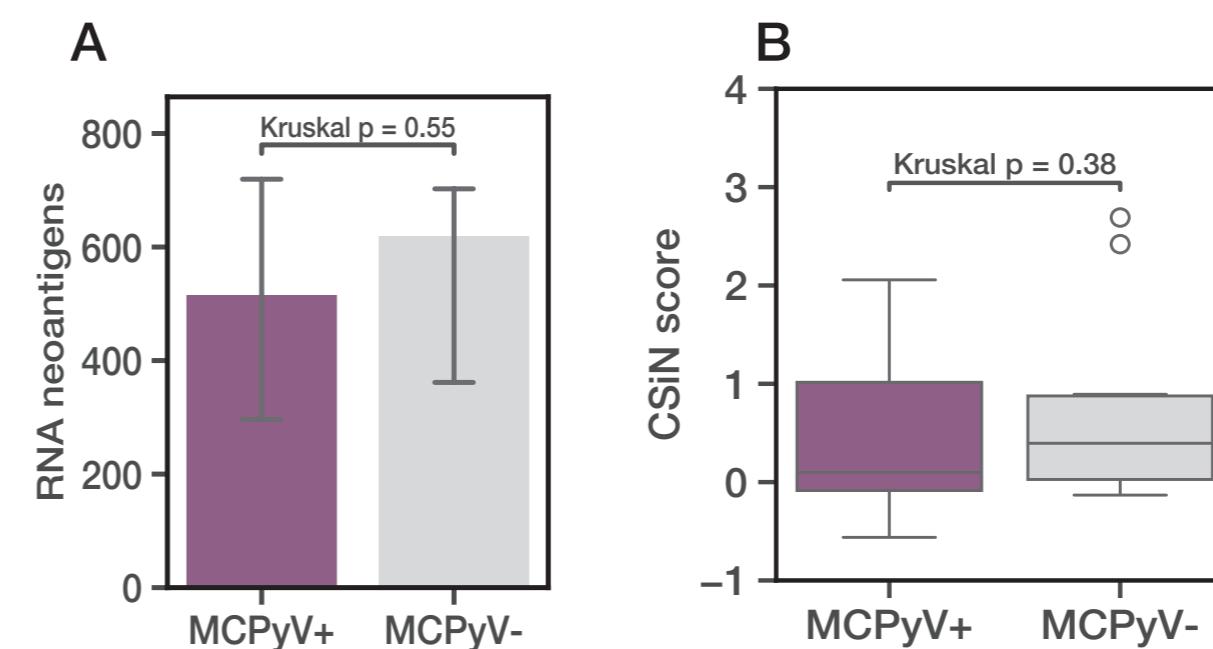


METHODS AND DATA

RNA was extracted and sequenced from 27 microdissected biopsies collected from a retrospective cohort of treatment naive MCC patients before starting anti-PD1 immunotherapy.

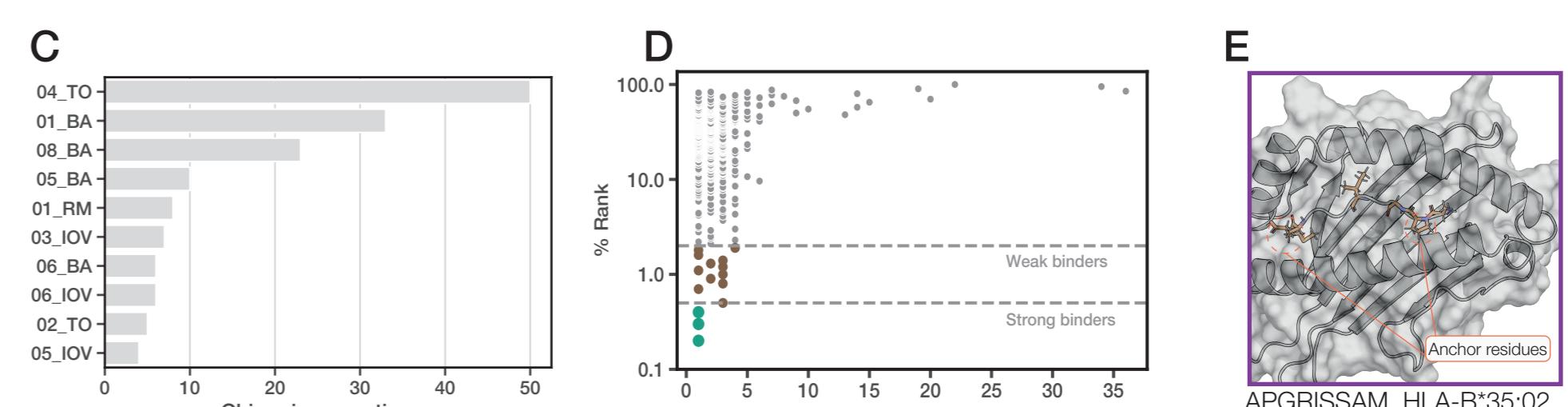


RESULTS

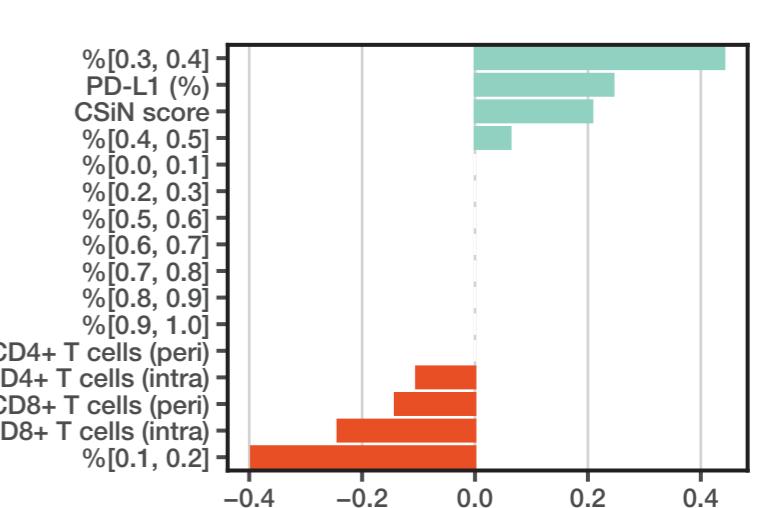


Neoantigens derived from somatic RNA-mutations does not differ significantly in both quantity (A) and quality, measured using the Cauchy-Schwarz index of Neoantigens (CSIN)⁴ score (B).

We identified a variable number of viral junctions across the cohort, leading to a diverse range of chimeric neoantigens (C). These neoantigens showed a favorable binding potential, as determined by the %Rank (D). We further confirmed the binding goodness of them via structural modeling of the pMHC complex (E).



Patients with a higher percentage of clonal neoantigens (VAF > 0.2) and elevated PD-L1 expression were more likely to respond to ICB therapy. Our logistic regression model suggests these factors are key markers of a pre-existing but stalled immune response that can be unlocked by ICB treatment.



CONCLUSIONS

- We implemented a integrated approach for **somatic/viral neoantigens prediction in MCC patients using just tumor RNA-seq**
- We reported **multiple neoantigens arising from chiral CDS**, opening for the route for highly-specific **personalized immunotherapies**

REFERENCES

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