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P2.S2.06: Functional Impact of Missense Mutations Affecting Immune Response Genes in Human Cancer

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INTRODUCTION



Tumor immune evasion limits the effectiveness of immunotherapies



Defects in HLA-I antigen presentation and IFN γ signaling are key mechanisms of resistance

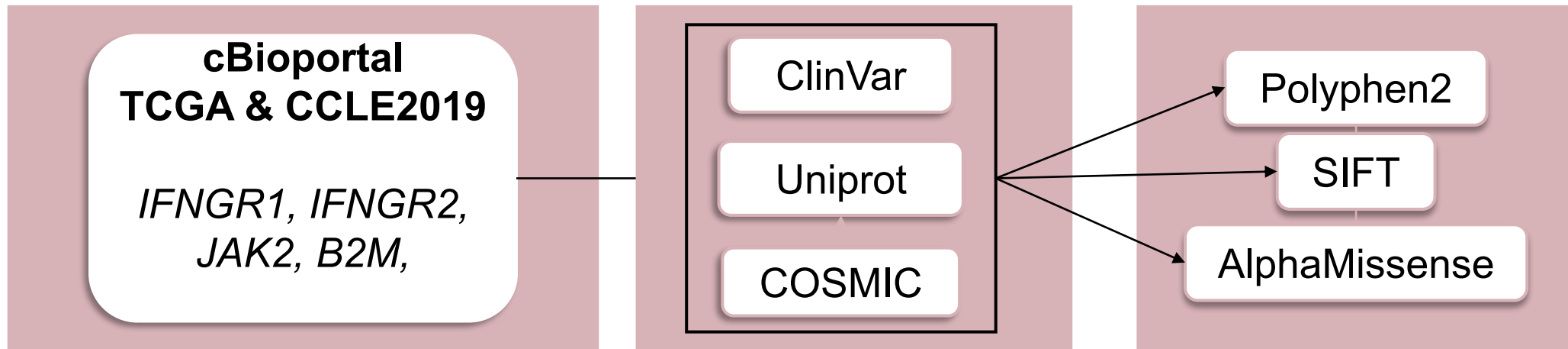


These alterations compromise T-cell recognition and the antitumor effects of IFN γ

Our study aims to characterize such tumor-intrinsic defects to improve response to immune checkpoint blockade

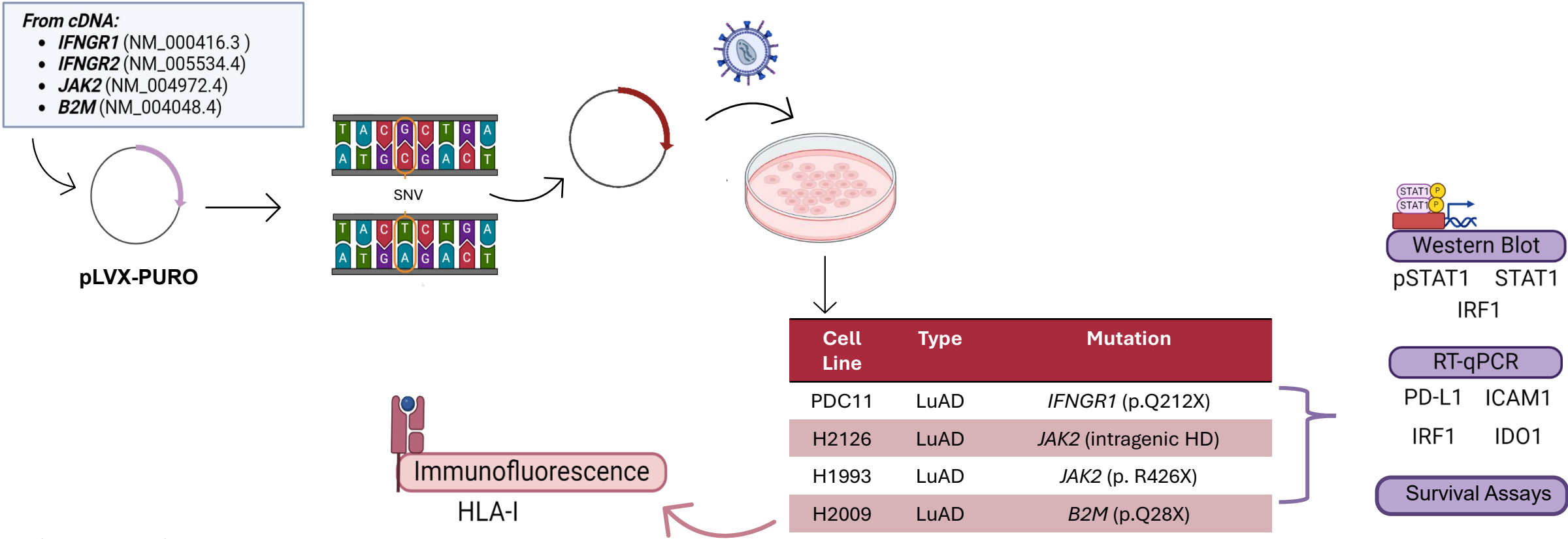
METHODS

Screening of missense mutations from Data Sets



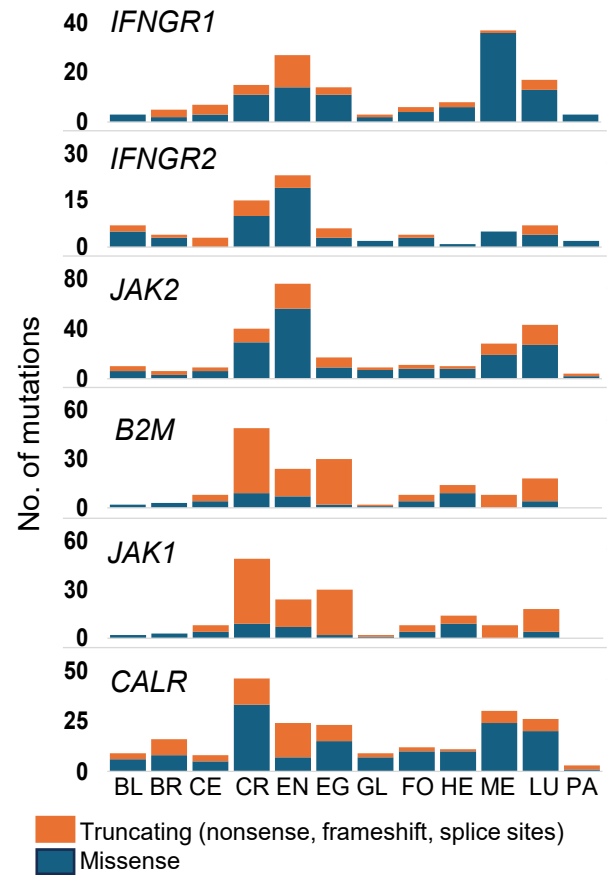
METHODS

Gene Cloning and Functional Effect Testing



RESULTS

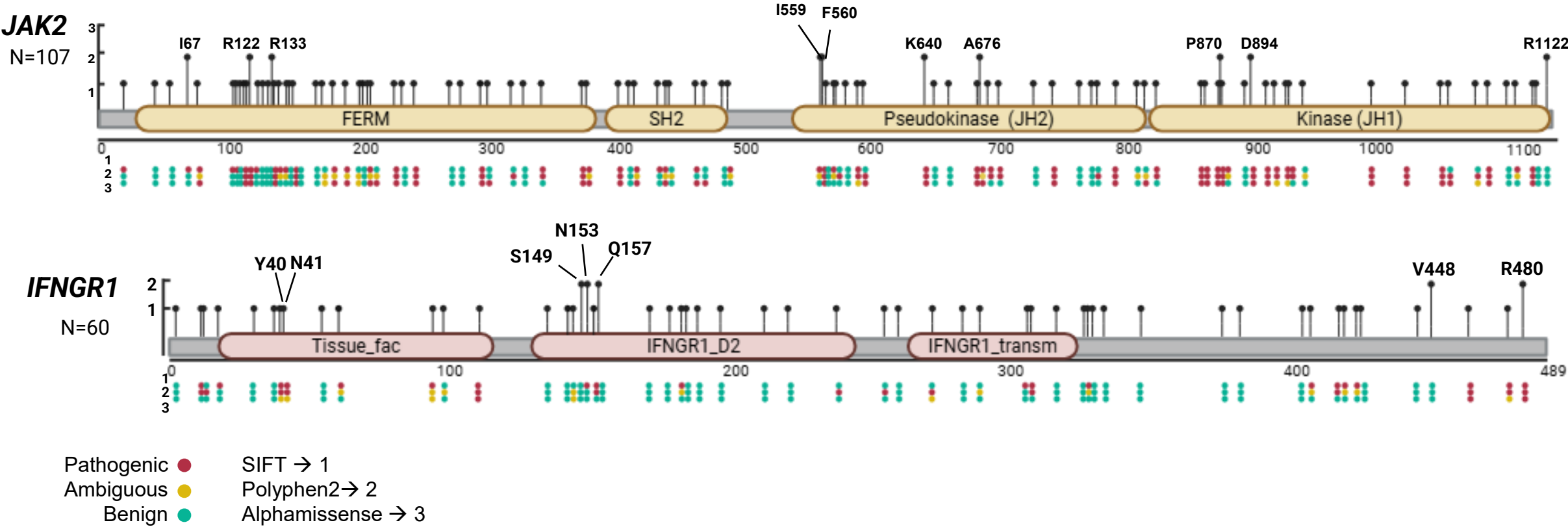
Mutational Profile of Components of the Immune Response in Human Cancer



(GL) Glioblastoma/glioma (n=1199)
(FO) Head & Neck/Oral cavity (n=587)
(HE) Hematologic (n=351)
(ME) Melanoma (n=554)
(LU) Lung (n=1311)
(PA) Pancreatic (n=241)
(BL) Bladder (n=455)
(BR) Breast (n=902)
(CE) Cervical (n=315)
(CR) Colorectal (n=678)
(EN) Endometrial (n=558)
(EG) Esophagogastric (n=708)

RESULTS

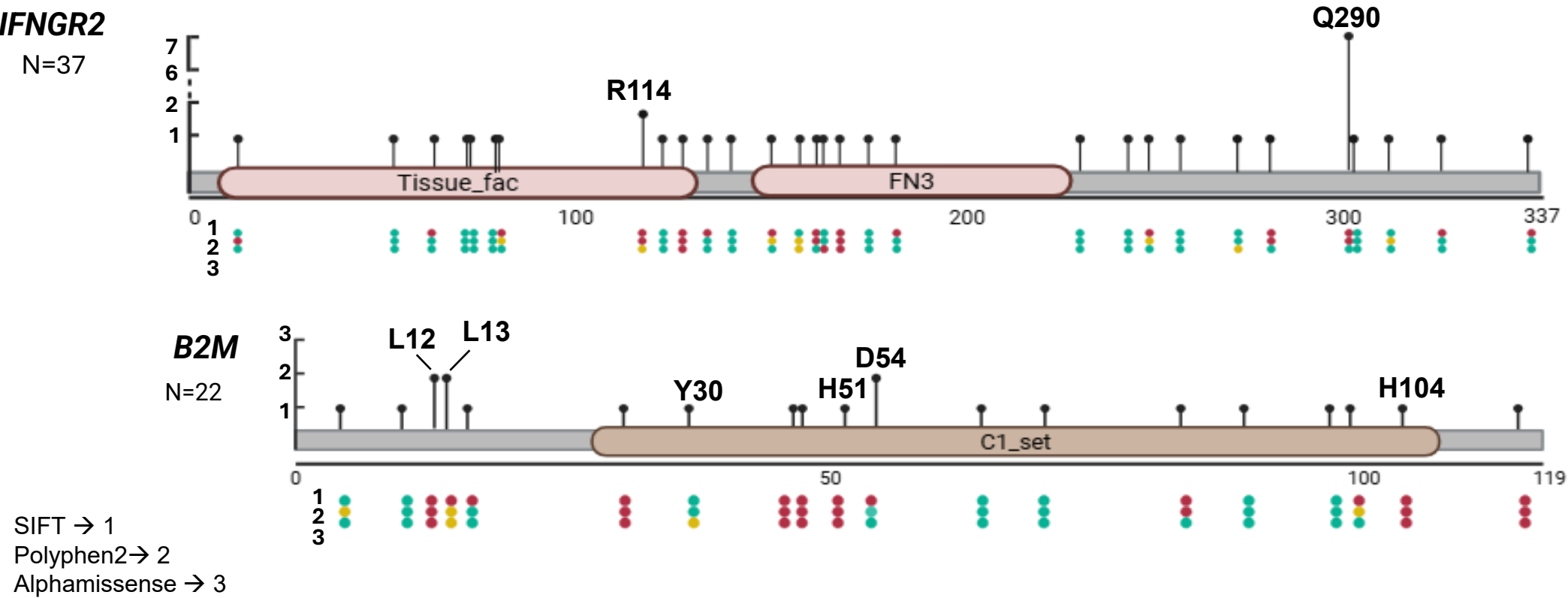
Computational Prediction of the Effects of Amino Acids Substitutions in Immune Respons-Related Genes



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RESULTS

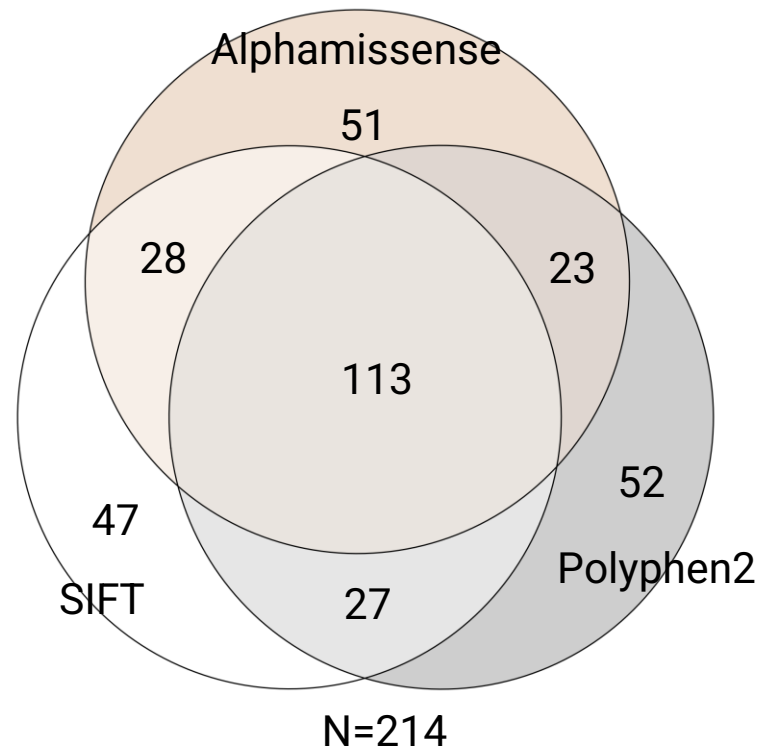
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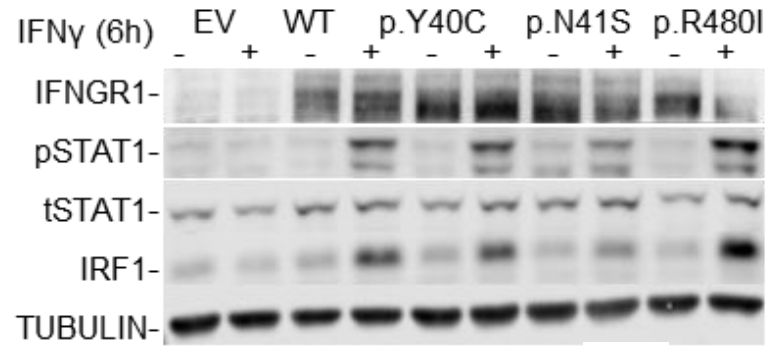
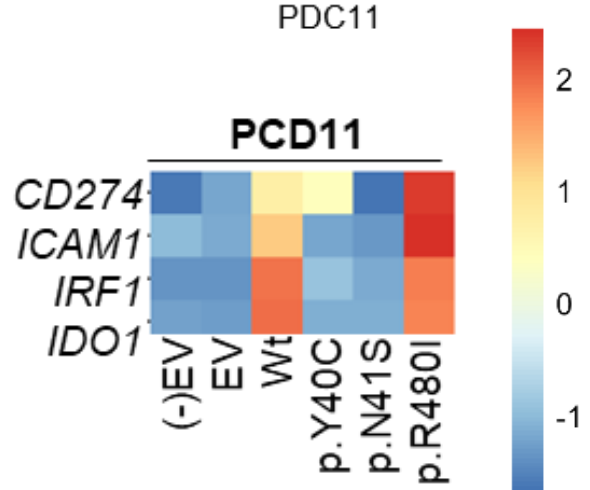
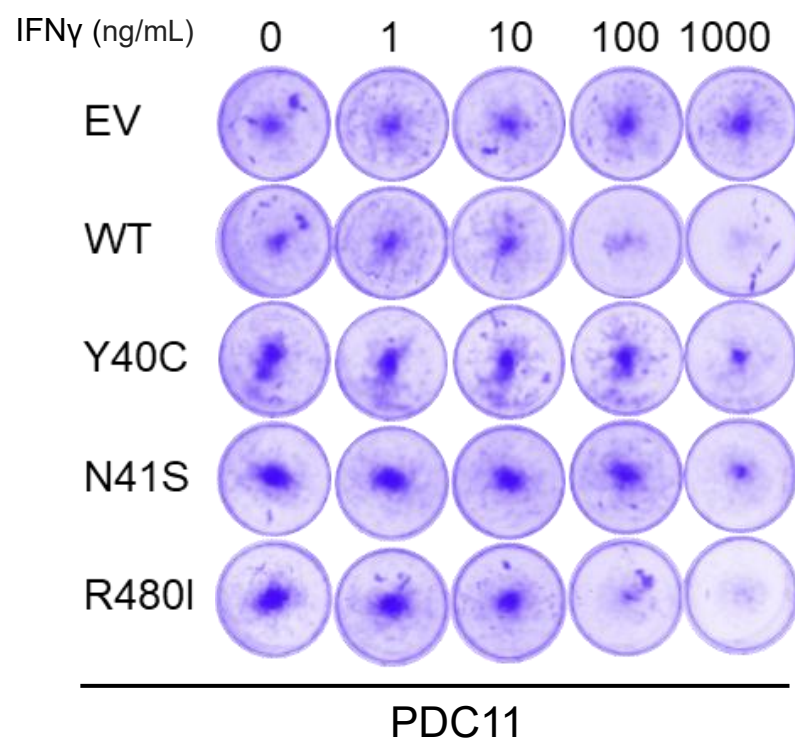
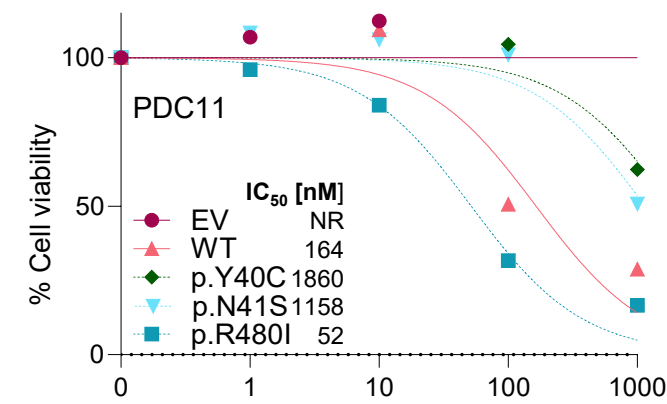
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Computational Prediction of the Effects of Amino Acids Substitutions in Immune Respons-Related Genes



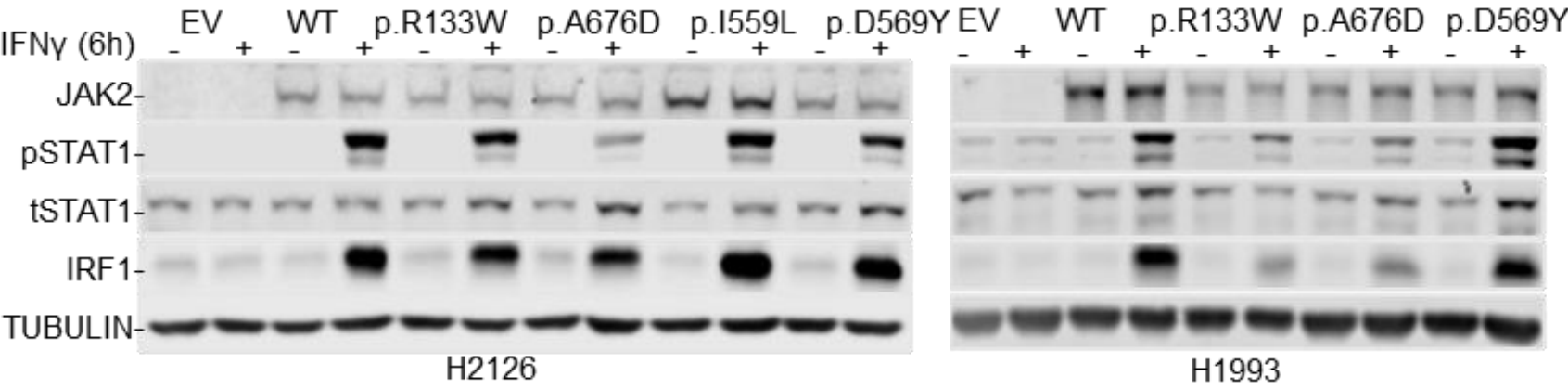
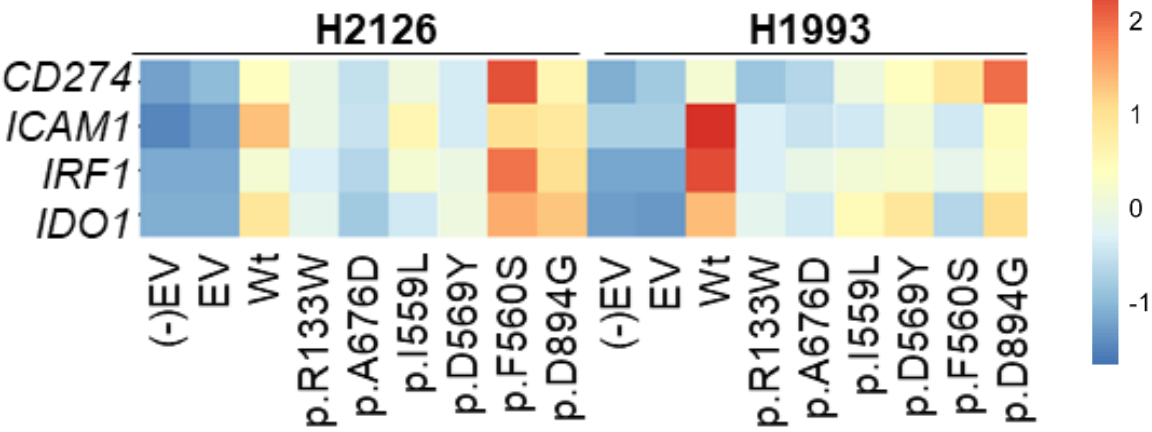
RESULTS

Functional Assessment of Amino Acid Substitutions at IFNGR1 and JAK2



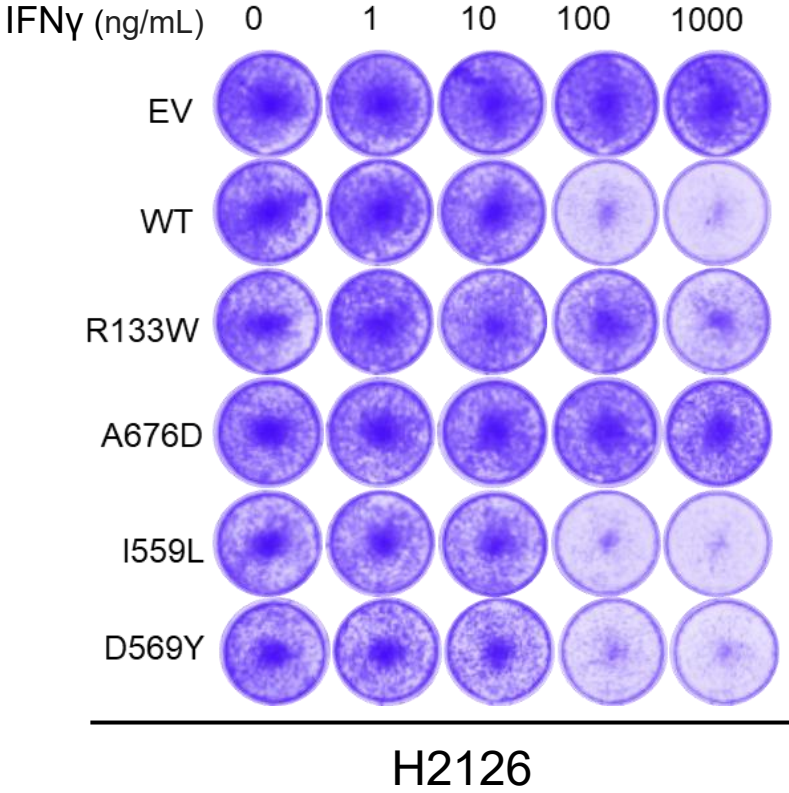
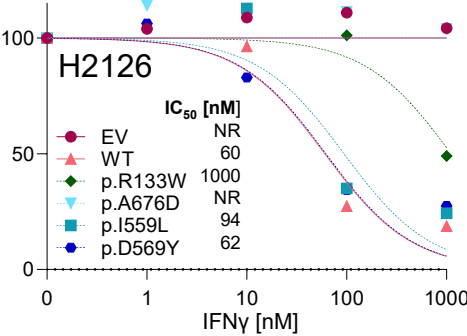
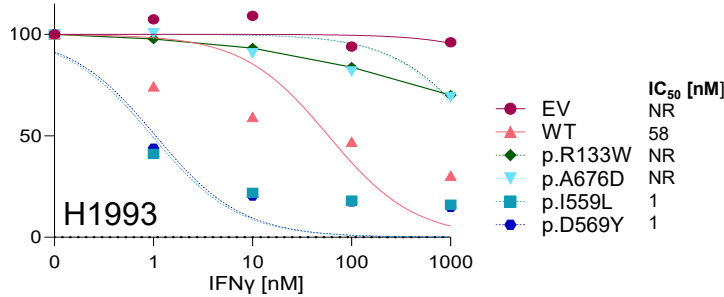
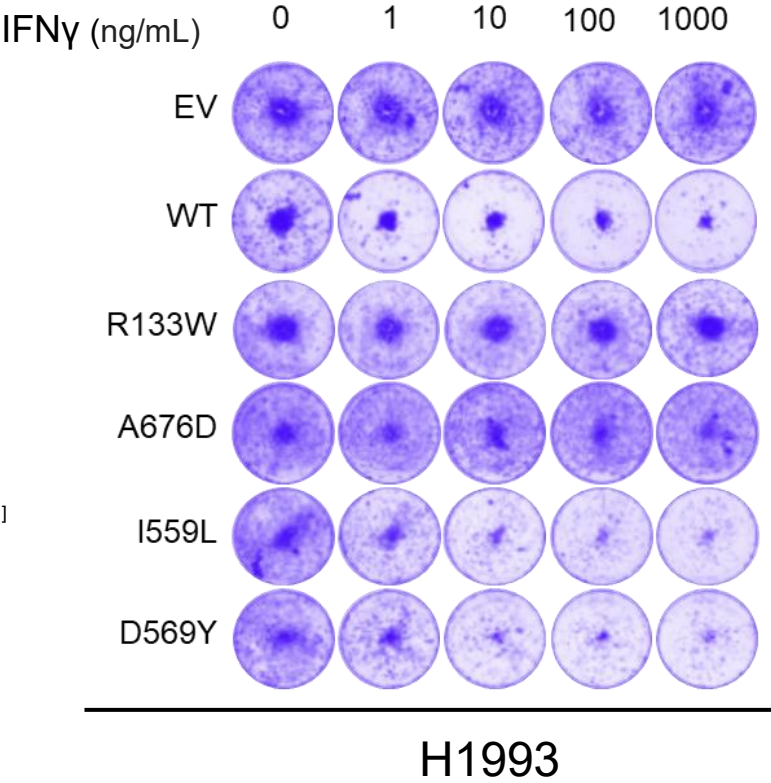
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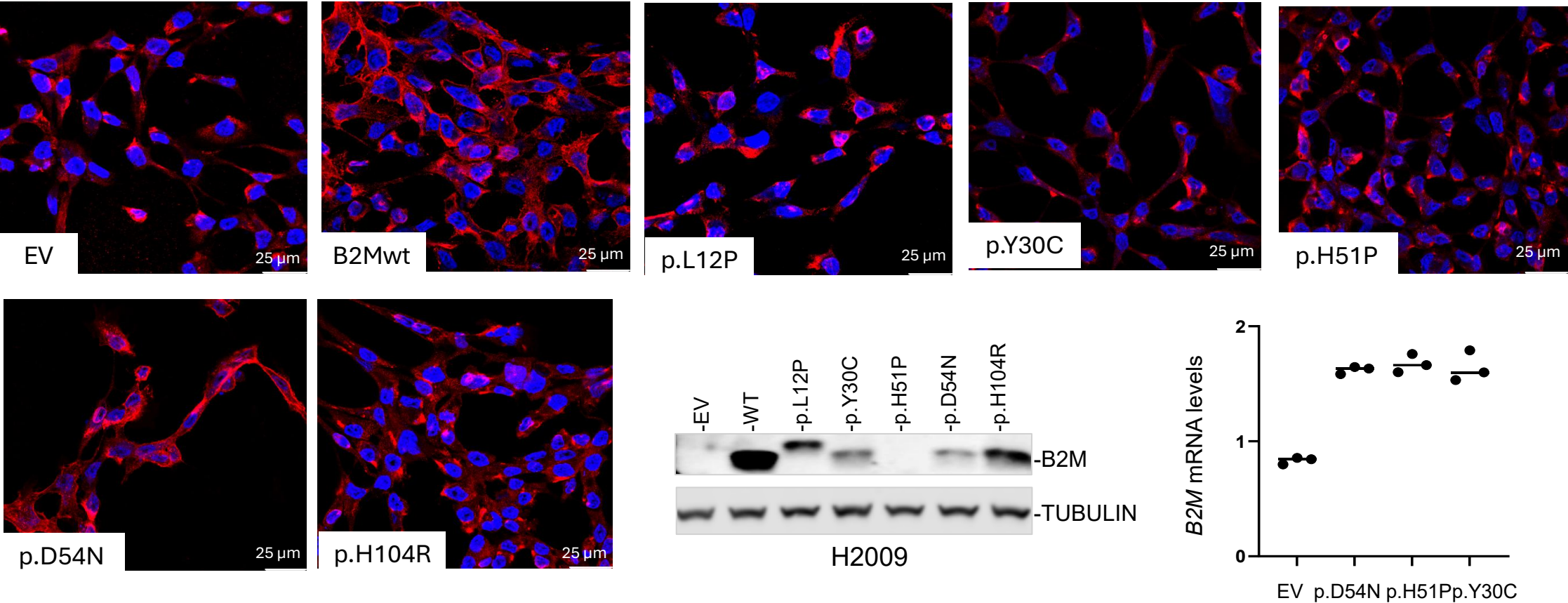
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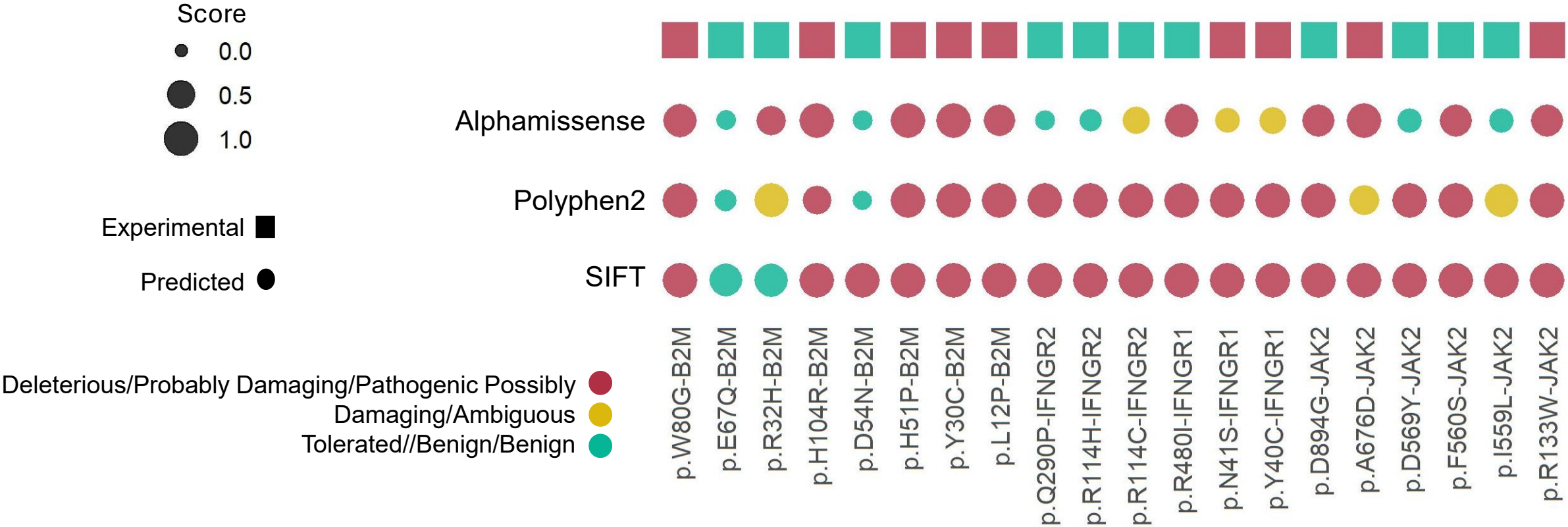
RESULTS

Assessment of Amino Acid Substitution functionality at B2M



RESULTS

Comparison of Predicted Effect by Indicated Algorithms and Functional Data Observed



DISCUSSION AND CONCLUSION



~10% of human cancers harbor mutations in *IFNGR1/2*, *JAK1/2*, *B2M* or *CALR*



Dysfunctional variants in **JAK2** and **IFNGR1** impair IFN γ signaling



B2M mutations frequently disrupt HLA-I antigen presentation, enabling immune evasion

Genetic alterations in IFN γ signaling and antigen presentation genes are frequent across cancers and can compromise immune surveillance. Including these genes in patient genetic screening may help predict immunotherapy benefit.



DISCUSSION AND CONCLUSION

Further studies should define the signaling thresholds required for effective IFN γ -mediated tumor suppression and explore how partial loss-of-function variants contribute to immune escape.

Clinical integration of these findings may improve patient stratification for immunotherapy.

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Thank You



CONQUERING LUNG AND OTHER THORACIC CANCERS WORLDWIDE IN THE 21ST CENTURY