Leveraging Deep Learning for Functional Analysis of Missense Mutations in Uveal Melanoma

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Purpose

- Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, characterized by a complex genetic landscape.
- We aim to enhance our understanding of UM by applying deep learning technologies to predict the pathogenicity of missense mutations and AlphaFold to visualize their structural impact.

Methods

- **Data Source:** Missense mutations frequently observed in UM were identified from the COSMIC database (Catalogue of Somatic Mutations in Cancer).
- **Prediction Tool:** Pathogenicity of these mutations was predicted using AlphaMissense, a deep learning model that calculates pathogenicity scores ranging from 0 (benign) to 1 (pathogenic).
- **Visualization:** The structural impact of mutations was visualized using AlphaFold, which predicts 3D protein structures
- **Clinical Validation:** Mutations were cross-referenced with clinical significance data from the ClinVar database to validate AlphaMissense predictions.

Results

- **Mutation Distribution:** Missense mutations accounted for 91.35% (n=1310) of all mutations in UM samples identified in COSMIC.
- GNAQ, GNA11, SF3B1, BAP1, and EIF1AX were identified as the most mutated genes.

Table 1. Frequency of Mutations in Key Genes Associated with Uveal Melanoma from COSMIC and Cross-validated with ClinVar.

Gene	Total Mutations	Samples Tested	Unique Mutations	Present in ClinVar (n)	Present in ClinVar (%)
GNAQ	588	1685	21	6	28.57%
GNA11	526	1429	13	4	30.77%
BAP1	311	887	83	46	55.42%
SF3B1	158	942	18	6	33.3%
EIF1AX	27	307	16	1	6.25%
	Total		151	63	41.72%

Table 2. Summary of confusion matrix results and performance metrics for AlphaMissense predictions compared to ClinVar annotations in uveal melanoma genes.

Gene	TP	TN	FP	FN	Sensitivity	Specificity
GNAQ	5	0	0	0	100%	N/A
GNA11	4	0	0	0	100%	N/A
BAP1	1	1	0	0	100%	100%
SF3B1	5	0	0	0	100%	N/A
EIF1AX	0	0	0	0	N/A	N/A

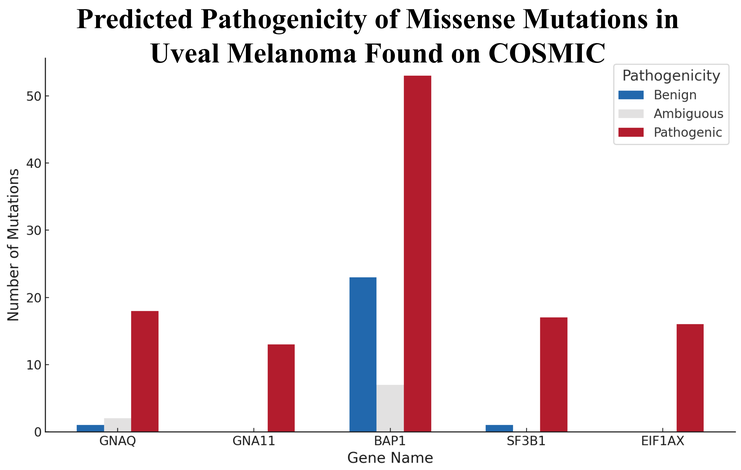

Figure 2. Predicted Pathogenicity of Missense Mutations Identified in Uveal Melanoma from the COSMIC Database Assessed Using AlphaMissense.

Conclusion

- **Deep learning tools** like AlphaMissense show promising accuracy in predicting the pathogenicity of missense mutations.
- **Clinical Relevance:** These findings may improve diagnostic precision and aid in developing personalized treatment strategies for patients with uveal melanoma by providing clearer insight into the functional consequences of genetic mutations.

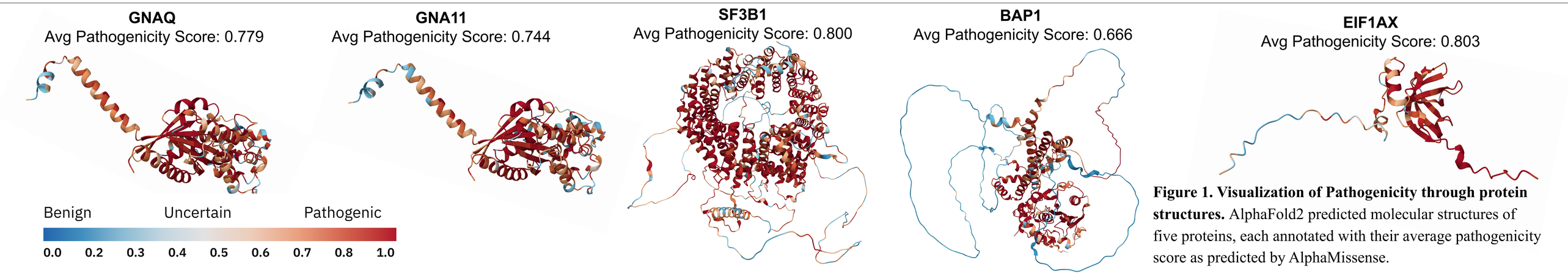

Figure 1. Visualization of Pathogenicity through protein structures. AlphaFold2 predicted molecular structures of five proteins, each annotated with their average pathogenicity score as predicted by AlphaMissense.