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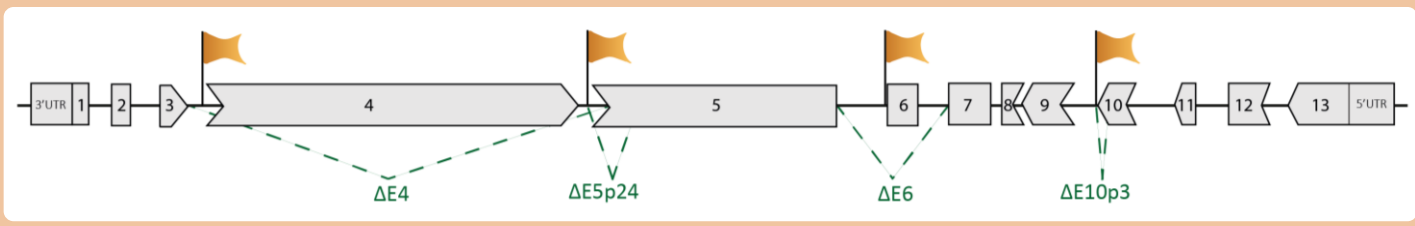
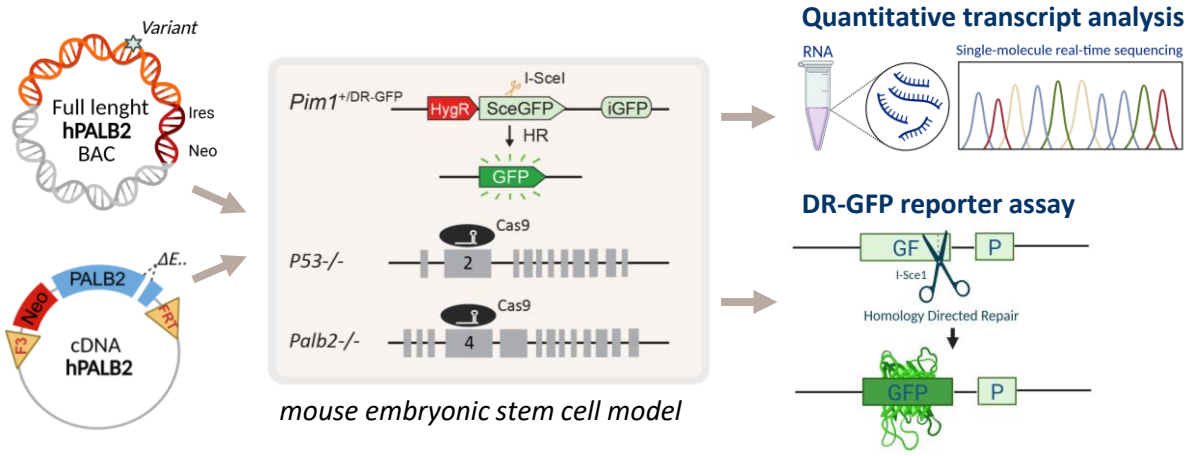
The Functional Impact of Spliceogenic Variants and Alternative Transcripts on PALB2 Tumor Suppression

Introduction. Clinical interpretation of predicted loss-of-function variants may be challenging as their functional impact depends on the functionality and relative expression of variant-induced transcripts. A mouse embryonic stem cell (mESC)-based assay was used to quantitatively assess the impact of human *PALB2* splice site variants on mRNA splicing and homologous recombination (HR) activity.

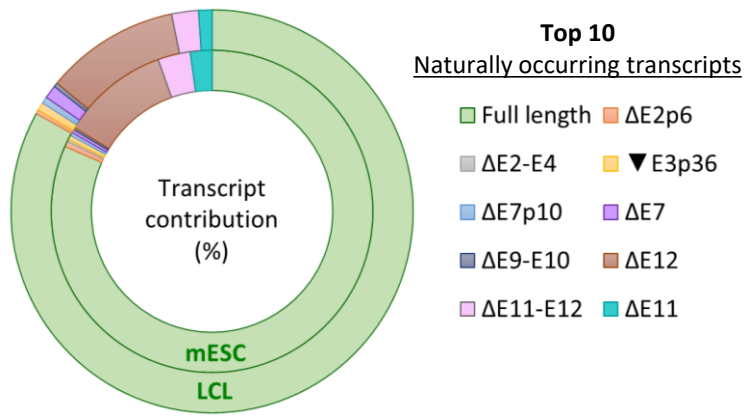
Conclusion. Caution is advised for the clinical interpretation of variants expressing ΔE4, ΔE5p24, ΔE6 and ΔE10p3 transcripts, as these encode functional protein isoforms (orange flags).



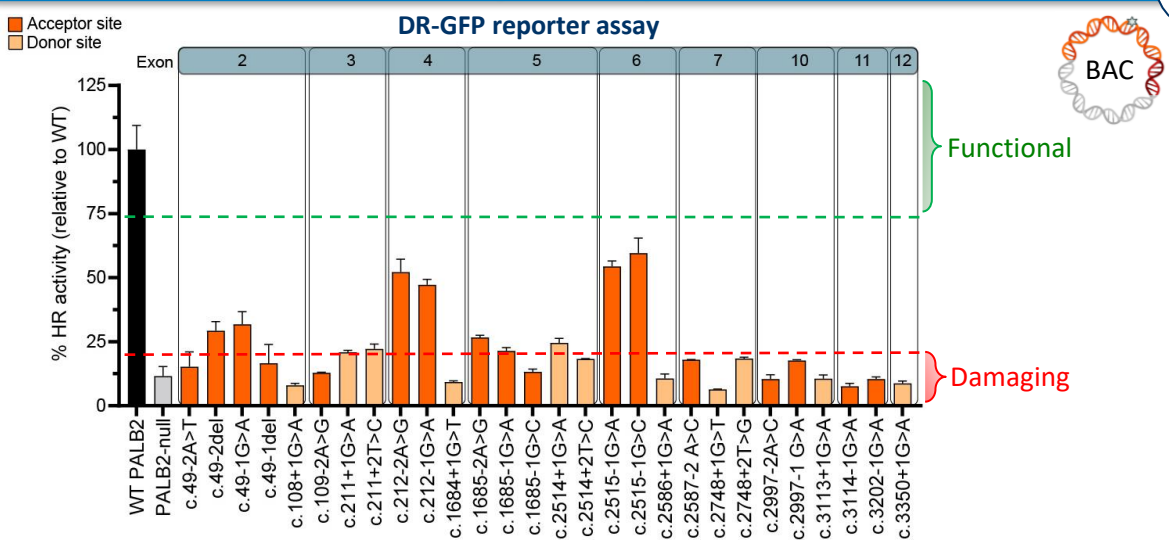
Mouse embryonic stem-cell based assay



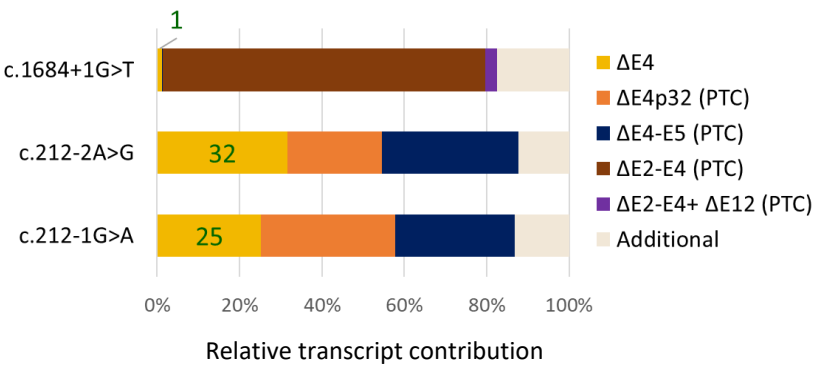
Transcript profile of human wildtype *PALB2*



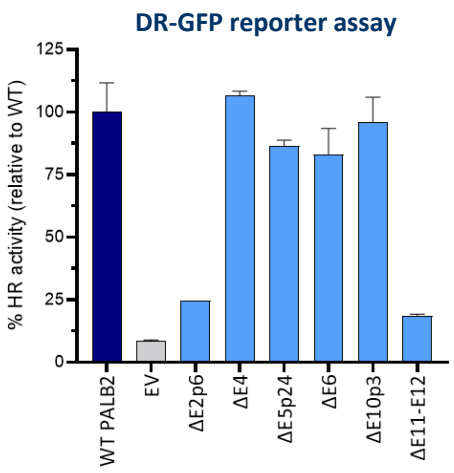
Functional impact of splice site variants

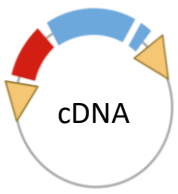


Transcript profile exon 4 splice site variants



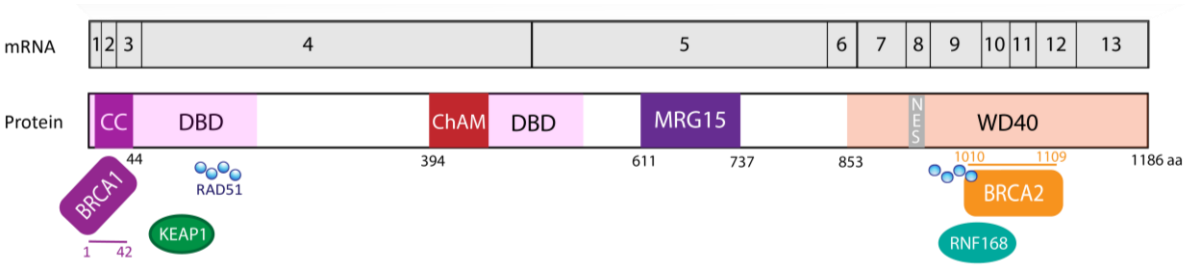
Functionality of naturally occurring isoforms





exclusive expression of alternative transcript

Functionality of potential rescue transcripts from Lopez et al., 2019 and our analysis.



Abbreviations

LCL: Lymphoblastoid Cell Line from healthy blood donor
PTC: Transcript with Premature Termination Codon
BAC: Bacterial Artificial Chromosome
EV= Empty Vector
mESC: mouse Embryonic Stem Cells
HR: Homologous Recombination
E= Exon
hPALB2= human *PALB2* gene

Pink Ribbon 11704
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BRCA 2025
Abstract 296

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