Isoform-Specific Loss of Function Variants in *CDKN2A* and Their Association with Cancer Phenotypes

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Background

- *CDKN2A* is a tumor suppressor gene that encodes two transcripts: p16INK (p16) and p14ARF (p14)

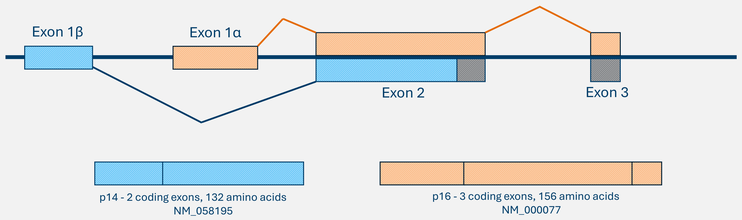


Figure 1: Depiction of genomic arrangement and exon nomenclature for *CDKN2A*. The p14 isoform of *CDKN2A* is transcribed starting in Exon 1β, while p16 begins in Exon 1α. Both transcripts use the same Exon 2 but encode different amino acids and have different reading frames. Exon 3 is non-coding for p14.

- Pathogenic, loss-of-function (LoF) variants in p16 are associated with familial melanoma-pancreatic cancer syndrome, historically known as familial atypical multiple mole melanoma syndrome (FAMMM)
- Large deletions that include all of *CDKN2A* as well as those isolated to Exon 1β impacting p14 have been observed to be associated with the development of tumors such as melanoma, astrocytoma, and neural sheath tumors[1,2]
- The phenotypic association with LoF nonsense/frameshift variants impacting only the p14 isoform is unclear

Methods

- A retrospective review of individuals who underwent multigene panel testing for hereditary cancer from 2015-2023 with LoF variants in either the p14 or p16 isoforms
- Nonsense, frameshift, initiation codon, and canonical splice variants as well as gross deletions were considered LoF
- Variants in the overlapping sequence that cause LoF in both isoforms, such as frameshifts, were categorized as p16 LoF
- Melanoma prevalence in the two groups was compared using the Chi Square Test

Results and Discussion

- A total of 258 individuals with 51 unique LoF variants were identified
- There were 192 individuals with p16 LoF variants and 66 individuals with p14 LoF variants
- LoF variants impacting p14 alone had significantly reduced rates of melanoma compared to p16 LoF variants
- Gross deletions and splicing variants impacting Exon 1β did show increased association, but it's possible these variants impact p16

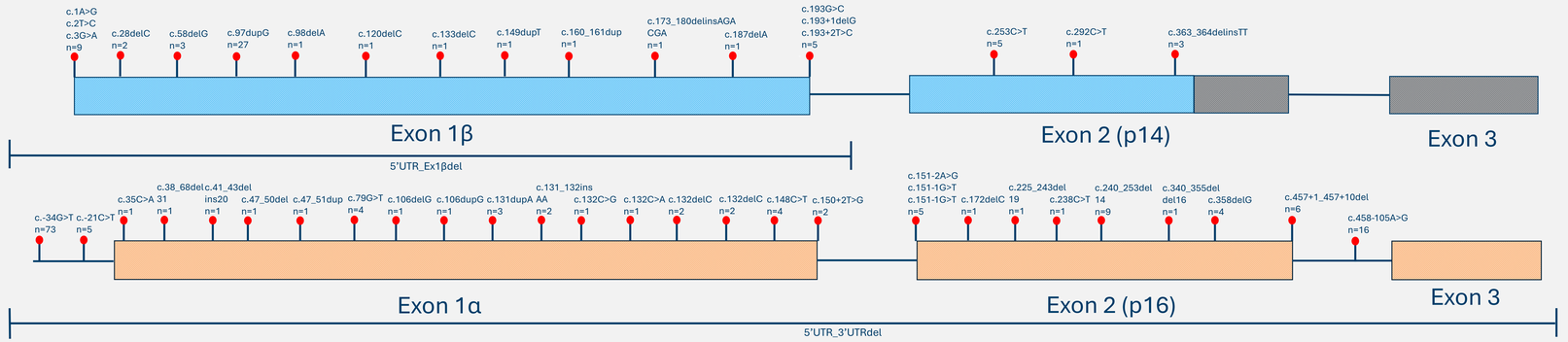
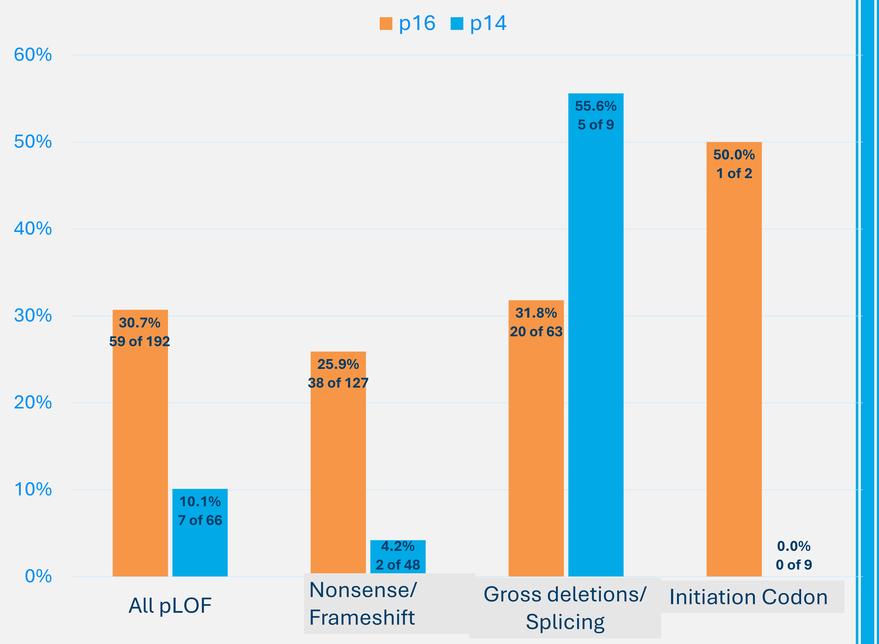


Figure 3. Melanoma Prevalence in Probands with LOF variants in p16 and p14



TAKE HOME POINTS

- Nonsense/frameshift variants impacting only the *CDKN2A* p14 isoform do not have a clear cancer association
- Splicing variants impacting Exon 1β of the p14 isoform have phenotype associated with melanoma-pancreatic cancer syndrome
- More work is required to characterize genotype-phenotype correlations for p14 variants