CDKN2A germline alterations and the relevance of genotype-phenotype associations in cancer predisposition

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Abstract

Although CDKN2A is well-known as a susceptibility gene for melanoma and pancreatic cancer, germline variants have also been anecdotally associated with a broader range of neoplasms including neural system tumors, head and neck squamous cell carcinomas, breast carcinomas, as well as sarcomas. The CDKN2A gene encodes for two distinct tumor suppressor proteins, p16INK4A and p14ARF, however, the independent association of germline alterations affecting these two proteins with cancer is under-appreciated. Here, we reviewed CDKN2A germline alterations reported among individuals and families with cancer in the literature, specifically addressing the cancer phenotypes in relation to the molecular consequence on p16INK4A and p14ARF. While melanoma is observed to associate with variants affecting both p16INK4A and p14ARF transcripts, it is noted that variants affecting p14ARF are more frequently observed with a heterogenous range of cancers. Finally, we reflected on the implications of this inferred genotype-phenotype association in clinical practice and proposed that clinical management of CDKN2A germline variant carriers should involve dedicated cancer genetics services, with multidisciplinary input from various healthcare professionals.

Keywords: CDKN2A, Cancer predisposition, p16INK4A, p14ARF

Background

CDKN2A (cyclin dependent kinase inhibitor 2A, OMIM 600160) is a tumor suppressor gene that encodes for two proteins, namely p16INK4A and p14ARF, critical for the regulation of cell cycle pathways. Genetic and epigenetic alterations inactivating CDKN2A are frequently encountered in a myriad of cancers, with base sequence-altering events more common in cancer types such as melanoma, head and neck squamous cell carcinoma (HNSCC), pancreatic cancer, lung cancer, esophageal cancer, and glioblastoma multiforme (GBM) [1–3]. Germline alterations in CDKN2A are most frequently associated with predisposition to melanoma and pancreatic cancer [4–8], detected through gene-panel testing in about 38% of melanoma-prone families [6, 9] but there have been sporadic reports implicating susceptibility to other neoplasms such as neural system tumors (NSTs), breast cancer, multiple myeloma, HNSCC, and sarcoma [10–18]. It is plausible that the varying cancer types reported with CDKN2A genetic alterations can be distinguished by the different variant effects on p16INK4A and p14ARF, although evidence to date are limited and conflicting [12, 13, 16, 19–21]. Here, we reviewed the spectrum of CDKN2A germline variants and associated neoplasms reported in literature, focusing on the relationship between distinct variant consequences on p16INK4A/p14ARF with the reported phenotypes. Variants evaluated include those detected in affected

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individuals through sequencing and/or classified as pathogenic or likely pathogenic in ClinVar database (version 2020-09-08, https://www.ncbi.nlm.nih.gov/clinvar/) without conflicts in interpretation.

**p16\(^{INK4A}\)/p14\(^{ARF}\) locus in the CDKN2A gene**

The **CDKN2A** gene spans 27.5 kb on chromosome 9p21 and is associated with over 10 transcript variants, of which the largest two encode for p16\(^{INK4A}\) and p14\(^{ARF}\) [22]. p16\(^{INK4A}\) is a 156 amino acid protein translated from a transcript of three exons (exons 1α,2,3; RefSeq NM_000077), known to negatively regulate cell cycle progression through inhibition of cyclin-dependent kinases [23]. The largest transcript produces p14\(^{ARF}\) (RefSeq NM_058195), a 132 amino acid protein, encoded via an alternative open-reading frame and first exon (exon 1β), with an established role of promoting p53 function through sequestration of MDM2 [24]. Consequently, p16\(^{INK4A}\) and p14\(^{ARF}\) are distinct proteins with different roles and no sequence homology, sharing only the use of same exons 2 and 3. Notably, although both tumor suppressors are encoded by three exons of similar size (exon1α: 421 bp, exon 1β: 486 bp, exon 2: 307 bp, exon 3: 490 bp), the bulk of translated sequence is localized to exon 1α/1β and exon 2.

**Spectrum of p16\(^{INK4A}\)/p14\(^{ARF}\) variants associated with neoplasms**

There are differences in molecular consequences of **CDKN2A** variants reported in literature on p16\(^{INK4A}\) and p14\(^{ARF}\), which is expected given the use of different open-reading frames. Most of the p16\(^{INK4A}\)-affecting variants are missense changes (28/55) followed by protein-disrupting variants (20/55, including truncating and null effects), occurring on exon 1α and exon 2 (Table 1). In comparison, almost one-third of these reported variants fall within intron 1 of p14\(^{ARF}\) transcript corresponding to exon1α of p16\(^{INK4A}\), followed by missense (16/62) and protein-disrupting (13/62) changes, which are mostly concentrated in exon 2 of p14\(^{ARF}\). Due to the difference in transcript architecture, there is an overall higher likelihood of encountering variants outside of protein sequence-coding regions (e.g. intronic, 3-prime untranslated region) in p14\(^{ARF}\) compared to p16\(^{INK4A}\).

Based on the distribution of reported neoplasms with germline **CDKN2A** variants in Table 1, the association with melanoma is evidently irrespective of variant consequence on both p16\(^{INK4A}\) and p14\(^{ARF}\). Variants affecting p16\(^{INK4A}\) coding transcript are more frequently observed with pancreatic cancer and HNSCC (23/55) compared to p14\(^{ARF}\) (8/29). This association is supported by an analysis of Dutch melanoma families demonstrating pancreatic cancer events in 58% of families with p16\(^{INK4A}\)-affecting variants but none among p14\(^{ARF}\)-affecting carrier families [87]. Intriguingly, a broader spectrum of cancers – e.g. uterine cancer, NSTs, GBM, non-Hodgkin’s lymphoma – is noted to co-occur with p14\(^{ARF}\)-affecting variants. Moreover, variants with a loss-of-function consequence exclusive to p14\(^{ARF}\), namely deletion of exon 1β, Glu33Glyfs*30 and Arg88*, were observed in individuals with adenocarcinomas of uterus, bladder and stomach, respectively. This apparent distinction of cancers observed with predicted loss either of p16\(^{INK4A}\) or p14\(^{ARF}\) function is congruent with the independent roles of both tumor suppressors in regulation of cell cycle progression and p53 pathway. In particular, the range of neoplasms co-occurring with p14\(^{ARF}\) variants is reminiscent of Li-Fraumeni syndrome, which is characterized by constitutional mutations in **TP53** and diminished p53 activity. Indeed, a dysregulated p53 pathway was observed exclusively in the malignant peripheral nerve sheath tumor (MPNST) of a germline CDKN2A deletion carrier diagnosed with synchronous HNSCC and MPNST [16]. It is also noteworthy that manifestations of neural system-related tumors such as MPNST, GBM, astrocytoma, and schwannoma were consistently reported together with families harbouring gross deletion of the **CDKN2A** locus and/or involving loss of an intact p14\(^{ARF}\) [12, 13, 16, 62, 88], suggesting a constitutional deficiency of p14\(^{ARF}\) associated with NSTs.

Collectively, these observed trends imply that **CDKN2A**-associated cancer susceptibility could be dependent on molecular consequence of the variant and affected transcript. While inferring this genotype-phenotype relationship is currently limited by the potential bias resulting from a p16\(^{INK4A}\)-centric focus in **CDKN2A**-related literature, an appreciation for this distinction in p16\(^{INK4A}\)/p14\(^{ARF}\) and larger case-cohort studies designed to address the causal effect of the specific variants will provide clarity in the future.

**Implications on clinical management**

Presently, clinical genetic testing for **CDKN2A** is indicated for individuals with multiple primary melanoma and/or a family history of melanoma or pancreatic cancer [89]. However, the expanded spectrum of phenotype accompanying germline alterations in **CDKN2A** suggests that it may be relevant to consider **CDKN2A** as a candidate for tumor predisposition beyond melanoma and pancreatic cancer in clinical practice. Indeed, numerous carriers of pathogenic/likely pathogenic variants (P/LPV) listed in Table 1 reported a variable family history of cancers, including sarcoma, leukemia, lymphoma, astrocytoma and cancers of the breast, lung, and prostate. It has been alluded that constitutional deficiency in **CDKN2A** phenotypically mirrors the broad tumor
| Exon/Intron | Nucleotide change | Protein change | Variant effect | Exon/Intron | Nucleotide change | Protein change | Variant effect | Neoplasms reported in variant carriers | References |
|-------------|------------------|----------------|---------------|-------------|------------------|----------------|---------------|--------------------------------------|-------------|
| Ex 1β | Del of Exon 1 | – | null | – | – | – | – | / | uterine adenocarcinoma, thyroid adenoma, chest wall neurilemmoma, pituitary macroadenoma | [21, 25] |
| Ex 1β | c.47G > A | Gly16Asp | MS | – | – | – | – | / | | [20] |
| Ex 1β | c.60_61insCGGCCGCGCGAGTG | Val22Profs*46 | PT | – | – | – | – | / | | [19] |
| Ex 1β | c.97dup | Glu33Glyfs*30 | PT | – | – | – | – | / | Bladder ca. | [26] |
| Ex 1β | c.161G > A | Arg54His | MS | – | – | – | – | / | | [27] |
| In 1 | c.193 +1G > A | Splicea | – | – | – | – | – | / | / | Multiple myeloma, brain tumor, colorectal ca. | [14, 36–40] |
| In 1 | c.194-3585C > A | n.d. | Int Ex 1 a c.33C > A | Ser12* | PT | / | | | | [41, 42] |
| In 1 | c.194-3576G > A | n.d. | Int Ex 1 a c.44G > A | Tyr15* | PT | / | | | | [25, 35, 42–44] |
| In 1 | c.194-3573T > G | n.d. | Int Ex 1 a c.47T > G | Leu16Arg | MS | / | | | | [4, 25, 29, 45, 46] |
| In 1 | c.194-3573T > C | n.d. | Int Ex 1 a c.47T > C | Leu16Pro | MS | / | | | | [9, 45–48] |
| In 1 | c.194-3553G > A | n.d. | Int Ex 1 a c.67G > A | Gly23ser | MS | / | | | | [45] |
| In 1 | c.194-3552G > A | n.d. | Int Ex 1 a c.68G > A | Gly23Asp | MS | / | | | | [25, 48–51] |
| In 1 | c.194-3549G > C | n.d. | Int Ex 1 a c.71G > C | Arg24Pro | MS | / | | | | [25, 32, 34, 51–53] |
| In 1 | c.194-3541G > T | n.d. | Int Ex 1 a c.79G > T | Glu27* | PT | / | | | | Neuroblastoma | [25, 54, 55] |
| In 1 | c.194-3525 T > C | n.d. | Int Ex 1 a c.95T > C | Leu32Pro | MS | / | | | | [18, 25] |
| In 1 | c.194-3514delG | n.d. | Int Ex 1 a c.106delG | Ala36Argfs*17 | PT | / | | | | [15] |
| In 1 | c.194-3489_194-3488insAA | n.d. | Int Ex 1 a c.131_132insAA | Tyr44* | PT | / | | | | [56–58] |
| In 1 | c.194-3488C > G | n.d. | Int Ex 1 a c.133C > G | Tyr44* | PT | / | | | | [56–58] |
| In 1 | c.194-3486del | n.d. | Int Ex 1 a c.132del | Tyr44* | PT | / | | | | [59] |
| In 1 | c.194-3478C > A | n.d. | Int Ex 1 a c.140C > A | Pro47Thr | MS | / | | | | [25] |
| In 1 | c.194-3477C > T | n.d. | Int Ex 1 a c.149C > T | Pro49Leu | MS | / | | | | [60] |
| In 1 | c.194-3474T > G | n.d. | Int Ex 1 a c.146T > G | Ile49Ser | MS | / | | | | [18, 25] |
| In 1 | c.194-3472C > T | n.d. | Int Ex 1 a c.148C > T | Gln50* | PT | / | | | | [32] |
| In 1 | c.194-3471A > C | n.d. | Int Ex 1 a c.149A > C | Gln50Pro | MS | / | | | | [52] |
| In 1 | c.194-69C > T | n.d. | Int In 1 c.151-69C > T | – | Int | / | (Uv) | | | [61] |
| In 1 | c.194-2A > G | n.d. | Splice | In 1 c.151-2A > G | n.d. | Splice | / | | | [18] |
Table 1  Pathogenic/likely pathogenic germline variants in CDKN2A affecting p16<sup>INK4A</sup> transcripts and the associated neoplasms reported in the literature (Continued)

| Exon/ intron | Nucleotide change | Protein change | Variant effect | Exon/ intron | Nucleotide change | Protein change | Variant effect | Neoplasms reported in variant carriers | References |
|--------------|-------------------|----------------|----------------|--------------|-------------------|----------------|----------------|---------------------------------------|------------|
| Ex 2         | c.202G > C         | Asp68His       | MS             |               | c.194-1G > C     | n.d.            | Splice<sup>a</sup> | / / / / Osteochondroma                  | [11, 13, 62]|
| Ex 2         | c.202G > A         | Asp68Asn       | MS             |               | c.199G > C      | Met53Ile        | MS             | / / / BrCa                              | [32]       |
| Ex 2         | c.210G > T         | Gin70His       | MS             |               | c.167G > T      | Ser56Ile        | MS             | / /                                   | [34, 35, 48, 63–65]|
| Ex 2         | c.215C > T         | Pro72Leu       | MS             |               | c.172C > T      | Arg58<sup>a</sup> | PT             | /                                     | [25]       |
| Ex 2         | c.219 T > G        | Ser73Arg       | MS             |               | c.176T > G      | Val59Gly        | MS             | / /                                   | [4, 30, 33, 64–66–68]|
| Ex 2         | c.237 T > C        | Ala79= Silent  |               |               | c.194 T > C     | Leu65Pro        | MS             | /                                     | [18, 25]   |
| Ex 2         | c.245_246delInsTT  | Arg82Leu       | MS             |               | c.202_203delInsTT | Ala68Leu       | MS             | / /                                   | [25]       |
| Ex 2         | c.255A > G         | Gin85= Silent  |               |               | c.212A > G      | Asn71Ser        | MS             | /                                     | [4, 59, 69, 70]|
| Ex 2         | c.256C > A         | Leu86Met       | MS             |               | c.213C > A      | Asn71Lys        | MS             | / / / Multiple myeloma                  | [17, 25]   |
| Ex 2         | c.262C > T         | Arg88* PT      |               |               | c.219C > T      | Ala73= Silent   |               | /                                     | [26]       |
| Ex 2         | c.268_286del / c.270_287del | Arg90Valafs*64 | PT             |               | c.225_243del / c.226_244del | Ala76Cysafs*64<sup>a</sup> | PT | / /                                  | [18, 25, 32, 44, 71–76]|
| Ex 2         | c.283_296del       | Thr95Leufs*61  | PT             |               | c.240_253del    | Pro81Cysafs*34  | PT             | / / / Papillary thyroid ca., uterine tumors | [77]       |
| Ex 2         | c.302C > T         | Pro101Leu      | MS             |               | c.259C > T      | Arg87Trp        | MS             | /                                     | [33, 55, 63, 78, 79]|
| Ex 2         | c.303G > C         | Pro11= Silent  |               |               | c.260G > C      | Arg87Pro        | MS             | / / /                                  | [10, 25, 69, 80]|
| Ex 2         | c.305G > T         | Gly102Val      | MS             |               | c.260G > T      | Glu88*          | PT             | /                                     | [33, 81]   |
| Ex 2         | c.320del           | Gly109Valafs*63 | PT             |               | c.283del        | Val93Glyafs*51  | PT             | /                                     | [46]       |
| Ex 2         | c.451_454delGGTG   | Ala152Glybfs*51 | PT             |               | c.327_380delGGTG | Leu97Glyafs*24  | PT             | / Low grade neuroepithelial tumor      | [53]       |
| Ex 2         | c.399G > C         | Pro113= Silent |               |               | c.296G > C      | Arg99Pro        | MS             | / / /                                  | [25]       |
| Ex 2         | c.344G > T         | Arg115Leu      | MS             |               | c.301G > T      | Gly101Trp       | MS             | /                                     | [18, 25, 32, 33, 67]|
| Ex 2         | c.350_351del       | Ala117Glyafs*43 | PT             |               | c.307_308del    | Arg103Glyafs*16 | PT             | / / /                                  | [25, 34]   |
| Ex 2         | c.365G > T         | Arg12Leu       | MS             |               | c.322G > T      | Asp108Yr        | MS             | / / /                                  | [82]       |
| Ex 2         | c.377C > G         | Pro126Arg      | MS             |               | c.334C > G      | Arg112Gly       | MS             | / / /                                  | [25]       |
| Ex 2         | c.378_380dup       | Ser127dup      | In-frame INS   |               | c.335_337dup    | Arg112dup<sup>+</sup> | In-frame INS | / / / non-Hodgkin’s lymphoma, cervical ca., phyllodes tumor | [10, 25]   |
| Ex 2         | c.382_383delInsCT  | Ala128Leu      | MS             |               | c.339_340delInsCT | Pro14Gsr        | MS             | /                                     | [63]       |
| Ex 2         | c.383_393del       | Ala128Gluafs*39 | PT             |               | c.340_351del    | Pro14Agaafs*27  | PT             | / / /                                  | [83]       |
| Ex 2         | c.2del             | –               | 3’UTR          |               | c.358del        | Glu120Serafs*26 | PT             | / / /                                  | [25, 67]   |
| Exon/intron | Nucleotide change | Protein change | Exon/intron | Nucleotide change | Protein change | Variant effect | Exon/intron | Nucleotide change | Protein change | Variant effect | Neoplasms reported in variant carriers | References |
|-------------|-------------------|----------------|-------------|-------------------|----------------|----------------|-------------|-------------------|----------------|----------------|-------------------------------------|------------|
| Ex 2        | c.*21 T > A       | –              | Ex 2        | c.377 T > A      | Val126Asp      | MS             | /           |                  |                |               | MEL PCa NST SARC BrCa HNSC LCa NFB Other neoplasms | [4, 9, 32, 48, 69, 70] |
| Ex 2        | c.*23 G > C       | –              | Ex 2        | c.379 G > C      | Ala127Pro      | MS             | /           |                  |                |               | /                                   | [52, 55, 84, 85] |
| Ex 2        | c.*101 G > T      | –              | Ex 2        | c.457 G > T      | Asp153Tyr      | MS             | /           |                  |                |               | /                                   | [52]       |
| In 2        | c.*102-105 A > G  | n.d.           | In 2        | c.458-105 A > G  | n.d.           | Int            | /           |                  |                |               | /                                   | [25]       |
|             | Del part of Exon 2| n.d.           | Del of Exon 1 & part of Exon 2 |                  |                | /             | /           |                  |                |               | /                                   | [86]       |
|             | Del of entire CDS | –              | Del of entire CDS |                  |                | /             | /           |                  |                |               | GBM, astrocytoma, meningioma [12, 16] |            |

Ex exon, In intron, CDS coding sequence, Del deletion, PT protein truncating, MS missense, INS in-frame insertion, Int intronic, 3UTR 3-prime UTR, ca. cancer, Mel melanoma, PCa pancreatic cancer, NST neural system tumors, Sarc sarcoma, BrCa breast cancer, HNSCC head and neck squamous cell carcinoma, LCa Lung cancer, NFB neurofibroma, Uvl uveal melanoma, NHL non-Hodgkin’s lymphoma, GBM glioblastoma multiforme, n.d. not determined.

a Splice site alteration is experimentally shown to result in protein truncation through exon skipping.

b Alternative names for NM_000077:c.-16_8dup (p.Ala4_Pro11dup) in the literature: 1_24dup, 23ins24, 32ins24, c.9_32dup24, c.24_47dup24, c.32_33ins24, c.32_33ins9_32, 24 bp duplication/insertion, pM1_58dup, p.1_8dup8

c Alternative name for NM_000077: c.148C > T (p.Gln50*) in the literature: 50Q > X

d Alternative name for NM_000077: c.172C > T (p.Arg58*) in the literature: p16INK4a Arg50Ter

e Alternative name for NM_000077: c.225_243del (p.Ala76Cysfs*64) in the literature: p16-Leiden

f Alternative names for NM_000077: c.335_337dup (p. Arg112dup) in the literature: 337-338insGTC, 113insR, 113insArg, p.R112.L113insR, 112-113insArg, p.Arg105ins
spectrum characteristic of Li-Fraumeni syndrome [13, 16, 18, 90], hence clinicians and genetic professionals should consider CDKN2A as a differential diagnosis for cancers such as HNSCC, NSTs, breast cancer, and sarcomas. One potential approach is to evaluate at-risk individuals with an assessment tool built upon a scoring system that accounts for the spectrum of personal and family history of cancers, such as one proposed tailored-approach for clinical management of hereditary melanoma [91]. Additionally, it is important to be mindful that identification of CDKN2A genetic alterations has been historically restricted to the p16\(^{INK4A}\) transcript, which would exclude the alternative coding region specific to p14\(^{ARF}\) (i.e. exon 1B). This could result in missed diagnoses especially for neoplasms potentially driven by p14\(^{ARF}\) deficiency, therefore it is imperative that genetic professionals comprehensively interrogate for alterations in both transcripts.

Current guidelines for clinicians managing individuals tested positive for CDKN2A germline P/LPV are directed towards surveillance for melanoma and pancreatic cancer. Carriers are recommended to undergo bi-annual comprehensive skin examination including scalp and genitalia by a dermatologist, supplemented with total body photography and dermoscopy [92, 93]. Earlier detection of melanoma and non-melanoma skin cancers have been demonstrated among carriers compliant to surveillance [94, 95], although larger cohort studies will be required to better evaluate the outcomes and factors influencing successful melanoma screening. Annual pancreatic surveillance with contrast-enhanced magnetic resonance imaging and/or endoscopic ultrasound is recommended for CDKN2A pathogenic variant carriers beginning age 40 years regardless of family history given their high lifetime risk [96] and emerging evidence supporting the potential for downstaging and improved 5-year overall survival [97–99]. Patients are also encouraged to adopt lifestyle modifications to reduce cancer risk, including regular exercise, healthy diet, limiting alcohol intake, practicing sun-smart behaviour and smoking cessation. Healthcare professionals caring for CDKN2A carriers should have a heightened index of suspicion for malignancies beyond melanoma and pancreatic cancer. Although there are currently no formal recommendations for surveillance beyond melanoma and pancreatic cancer, clinicians should monitor the presentation of neoplasms within patients’ families and consider individualized discussion on the risk and benefit of screening, especially for prevalent cancers. Additionally, at-risk family members should be offered familial genetic testing given that up to 44% of relatives of index patients carry the familial variant, of whom 96% were observed to comply with surveillance [100]. Considering the broad range of management strategies, a multidisciplinary approach to care through a centralized cancer genetics service will benefit these patients [101].

With the rapid uptake of multigene panel testing in clinical setting, new data will continuously re-frame our understanding on the genotype-phenotype associations relevant to CDKN2A. This is exemplified by a recent analysis evaluating the clinical phenotype and molecular results of hereditary cancer predisposition testing in 165,000 individuals, which revealed an association of germline CDKN2A pathogenic variants with increased risk for breast cancer (odds ratio: 3.35, 95% CI: 1.43–7.75) [102]. Clinicians should keep abreast with the constant updates given that this is an evolving field and that clinical management of individuals harbouring germline CDKN2A variants will likely recalibrate with time.

**Conclusion**

Cancer susceptibility among germline variant carriers of CDKN2A extend beyond the well-known predisposition to melanoma and pancreatic cancer, potentially associated with a multitude of cancers. The spectrum of associated cancer types may be driven by specific molecular consequences on p16\(^{INK4A}\) and/or p14\(^{ARF}\), warranting validation in future studies. Clinicians and genetic professionals should be cognizant of this expanded range of phenotypes and consider CDKN2A as a candidate gene for tumor predisposition syndrome in individuals and families presenting with such broad spectrum of cancers.

**Abbreviations**

bp: Base pairs; CI: Confidence interval; GBM: Glioblastoma multiforme; HNSC: Head and neck squamous cell carcinoma; kb: Kilobase; MPNST: Malignant peripheral nerve sheath tumor; NST: Neural system tumor; P/LPV: Pathogenic/likely pathogenic variants

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