Review Article

Germline Pathogenic Variants in Squamous Cell Carcinoma of the Head and Neck

(head and neck carcinoma / germline testing / oncogenetics / personalized medicine / familial hereditary syndrome)

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Abstract. Head and neck squamous cell carcinoma (HNSCC) presents a significant global health problem with variable geographic distribution and risk factors, including tobacco and alcohol abuse, human papillomavirus infections, and genetic predisposition. While the majority of cases are sporadic, several well-defined hereditary syndromes have been associated with a higher risk of developing HNSCC including Li-Fraumeni syndrome, Fanconi anaemia, Bloom syndrome, familial atypical multiple mole melanoma, and dyskeratosis congenita. There is also evidence of familial clusters of HNSCC, suggesting a genetic component in the development of the disease. Germline genetic testing in HNSCC using next-generation sequencing has revealed a wide range of germline variants, some of which were not anticipated based on standard guidelines. These variants may influence treatment decisions and have the potential to be targeted with precision medicine in the future. Despite these advances, routine germline genetic testing for HNSCC is not currently recommended and remains reserved for HNSCC cases with early onset or strong family cancer history. However, the increasing availability of germline genetic testing warrants development of more comprehensive and standardized testing protocols. Germline genetic testing also has the potential to influence precision-guided treatment in HNSCC patients carrying germline pathogenic variants.

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Abbreviations: BS – Bloom syndrome, CKI – checkpoint kinase inhibitor, DC – dyskeratosis congenita, EBV – Epstein-Barr virus, FA – Fanconi anaemia, FAMMM – familial atypical multiple mole melanoma syndrome, GPVs – pathogenic/likely-pathogenic variants, GWAS – genome-wide association study, HLA – human leukocyte antigens, HNSCC – head and neck squamous cell carcinoma, HPV – human papillomavirus, LFS – Li-Fraumeni syndrome, MEN – multiple endocrine neoplasia, NPC – nasopharyngeal carcinoma, PARP – poly(adenosine diphosphate-ribose) polymerase, PRS – polygenic risk scores, RT – radiotherapy, SCC – squamous cell carcinoma, TSG – tumour suppressor genes, XP – xeroderma pigmentosum.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the ninth most frequent cancer diagnosis (gco.iarc.fr) in both females and males with the incidence of 650,000 cases worldwide (Sung et al., 2020). It includes tumours derived from mucosal epithelium of the oral cavity, larynx and pharynx. In the Czech Republic, more than 1,800 cases are diagnosed annually. Moreover, the overall incidence of HNSCC cases is increasing rapidly. Between 2011 and 2021, a 31.5 % increase in incidence was observed in the Czech Republic (Institute of Health Information and Statistics of the Czech Republic, 2019). The vast majority of HNSCCs are sporadic; nevertheless, there are a few well-described and well-defined rare hereditary syndromes associated with increased HNSCC risk (Claus, 1995).

As we have entered the era of genomic medicine, the aim of this article is to summarize the advances in genetics and genomics, particularly germline testing in HNSCC, and to determine their impact on the daily practice.

Sporadic HNSCC

The most HNSCC cases arise as a sporadic disease caused by a life-long accumulation of acquired genetic and epigenetic changes. These are facilitated in the case of HNSCC by several life-style and environmental risk factors including tobacco use, alcohol consumption, infection of human papillomavirus (HPV) for oropharyngeal cancer, or Epstein-Barr virus (EBV) infection for nasopharyngeal cancer.

The main HNSCC risk factors are smoking in combination with alcohol abuse. Smoking (cigarettes, pipes, cigars) increases the risk more than five times compared to never smokers, similarly as alcohol consumption (Wyss et al., 2013). Nevertheless, it is difficult to separate the effects of smoking and alcohol; they appear to interact, multiplying the effect on the HNSCC risk (Lewin et al., 1998). Dal Maso et al. (2016) showed that the exposure to ethanol and/or cigarettes led to a steeply increasing risk of HNSCC, up to a 35 times higher risk compared to non-smokers and abstainers in the group of people who consumed high amounts of ethanol (84 g/day) and cigarettes (10 g/day) (Dal Maso et al., 2016). On the other hand, low or moderate alcohol consumption (10–19 g/day) had little or no effect among non-smokers (Lewin et al., 1998).

The role of HPV (primarily types 16 and 18) in developing HNSCC has been well-established in the last few decades. HPV-associated HNSCCs most commonly occur in the base of the tongue and in the tonsils. They typically affect younger patients with no history of tobacco or alcohol abuse (Fakhry et al., 2008; Vokes et al., 2015). Human papillomavirus-associated (HPV^+) oropharyngeal carcinoma is a rapidly emerging disease with a good prognosis, and that is why The International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) developed a TNM classification specific to HPV^+ oropharyngeal carcinoma, considering the uniqueness of this disease (Fakhry et al., 2008; Ang et al., 2010; O'Sullivan et al., 2016).

Histopathologically, squamous cell carcinoma (SCC) can be divided into keratinizing and non-keratinizing subtypes. This pathological subclassification becomes important in HNSCC mainly in the context of HPV-associated tumours, where a higher association of the non-keratinizing type with HPV infection has been reported (Ji et al., 2011; Chernock, 2012).

In the context of nasopharyngeal carcinoma (NPC), there is a marked geographical disproportion, with more than 70 % of new cases occurring in East and Southeast Asia, while in most other regions, NPC is considered a rare tumour with an incidence of less than 1/100,000 (Chen et al., 2019; Yu et al., 2022).

Despite the fact that the high prevalence of tobacco and alcohol abuse is high in the general population, only a small proportion of people with these predisposing life-style factors will develop HNSCC. Similarly, although the majority of sexually active people will be infected with HPV in their lifetime (and around 50 % of HPV infections involve certain high-risk types of HPV), most of these infections do not lead to cancer; only about 5 % of human tumours are caused by one of the high-risk HPV types (Haedicke and Iftner, 2013; Malik et al., 2023). This suggests individual susceptibility to tumour development due to inherited genetic variability.

Genetic testing

It is essential to distinguish between somatic and germline testing. Somatic testing refers to genetic testing of malignant cells, typically from a tumour specimen, and can identify pathogenic/likely-pathogenic variants (GPVs) that contribute to tumorigenesis, have a prognostic or predictive value, directing the use of targeted therapeutic agents. HNSCCs are generally characterized by a high mutational diversity (Cancer Genome Atlas Network, 2015).

Contrary to somatic genetic testing, germline genetic testing examines permanent heritable genetic information from "normal", non-cancer tissue (e.g., peripheral blood lymphocytes) in order to identify germline GPVs. Historically, GPVs had not played a role in the treatment selection, but this has changed since 2014, when poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor olaparib was introduced for the treatment of patients with ovarian cancer harbouring germline *BRCA1/2* variants (Kim et al., 2015). In a pan-cancer analysis (including HNSCCs), 8 % of patients with advanced cancers (about 16 % of the group of "other tumours" including HNSCC patients) harboured a GPV with therapeutic potential (Stadler et al., 2021).

Germline genetic alterations can also alter the tolerability of treatment. For example, radiotherapy (RT) is very often part of the HNSCC treatment. GPVs in genes involved in DNA repair explain accelerated carcinogenesis and increased radiosensitivity. Most radiosensitivity syndromes are autosomal recessive (e.g., ataxia telangiectasia, Nijmegen breakage syndrome, xeroderma pigmentosum, Cockayne syndrome, Bloom syndrome, and Werner syndrome) and RT is relatively contraindicated in most homozygous patients with these syndromes. Asymptomatic heterozygotes may have an increased risk of tumours, and a small proportion of patients may have a slightly increased risk of RT intolerance, but this does not limit the indication for RT (Lohynská et al., 2022, Argalácsová et al., 2023).

Somatic genetic landscape

The HNSCCs exhibit a high degree of genomic instability, as demonstrated in an analysis of 279 HNSCCs (243 HPV-negative and 36 HPV-positive) (Cancer Genome Atlas Network, 2015). In contrast to the percentage of mutations in individual genes in the COSMIC analysis ("upper aerodigestive tract" tissue), the most frequently mutated genes in The Cancer Genome Atlas

(TCGA) analysis were *TP53* (72 %), *FAT1* (23 %), *CDKN2A* (22 %), *PIK3CA* (21 %), *NOTCH1* (19 %), and *KMT2D* (18 %) (Cancer Genome Atlas Network, 2015; Tate et al., 2019). Alterations of these tumour suppressor genes (TSGs) are largely restricted to HPV-negative tumours. Mutational profiling revealed that HNSCC-associated pathogenic variants are significantly enriched in 11 genes, including *TP53*, *CDKN2A*, *FAT1*, *NOTCH1*, *KMT2D*, *NSD1*, and *TGFBR2*. However, HPV-positive tumours uniquely show frequent loss of *TRAF3*, *E2F1* amplification, frequent focal deletions in other TSGs (such as *NSD1*, *FAT1*, *NOTCH1,* and *SMAD4*), and frequent amplification of receptor tyrosine kinase genes, including *EGFR*, *HER2,* and *FGFR1*. Pathogenic variants in the genes encoding NRF2 and KEAP1, key regulators of oxidative stress, are also common and occur exclusively in HPV-negative HNSCC (Cancer Genome Atlas Network, 2015).

Familial/hereditary syndromes with HNSCC manifestation

The overall probability of cancer development is significantly increased in individuals carrying a GPV in cancer predisposition genes (Rahman, 2014). However, there are only very limited data describing GPVs of cancer-predisposing genes in HNSCC patients. Bychkovsky et al. (2022) performed germline genetic testing of *BRCA1*, *BRCA2*, and *PALB2* in different cancer types including 216 HNSCC cases and found 10 (4.6 %) patients carrying GPVs. Velleuer and Dietrich (2014) reviewed the data about HNSCC development in patients with Fanconi anaemia (FA). Tumours associated with GPVs in cancer predisposition genes occur at a younger age, mostly with minimal exposure to major extrinsic risk factors (HPV, tobacco, and alcohol).

The 5th edition of the WHO Classification of Head and Neck Tumours established a new section dedicated to hereditary syndromes with tumours and other lesions in the head and neck region, describing the main characteristics and manifestations of 15 syndromes (Nosé and Lazar, 2022; World Health Organization, 2022). We would especially like to highlight the Li-Fraumeni syndrome, Fanconi anaemia, familial atypical multiple mole melanoma, Bloom syndrome, and dyskeratosis congenita. All the syndromes are very rare.

The Li-Fraumeni syndrome (LFS) is an autosomal dominant cancer predisposition syndrome caused by a GPV in the *TP53* gene. The p53 protein is a transcription factor that regulates a large number of target downstream genes important in cell cycle arrest, DNA repair, and apoptosis in response to cellular stress signals such as DNA damage. Alterations of p53 represent the most frequent genetic events in human malignancies. The lifetime risk of cancer in individuals with LFS is ≥ 70 % for men and ≥ 90 % for women (Kumamoto et al., 2021). LFS is most commonly associated with five "core" tumours: breast, brain, soft tissue, adrenocortical carcinoma, and bone sarcoma (Guha and Malkin, 2017). In a retrospective analysis of 40 patients with LFS, 27 tumours were identified in 20 paediatric patients, of which 22 % (6/27) were primary or secondary tumours in the head and neck region, all soft tissue sarcomas in nature (Rodriguez et al., 2021). The increased incidence of HNSCCs associated with LFS has not been specifically described and quantified, but due to the approximately 40 % higher risk of secondary malignancies in the form of soft tissue sarcomas and/or basaloid squamous cell carcinomas in the area after previous radiotherapy (i.e., radiotherapy-induced tumours), the GERMLINE monitoring protocol recommends regular annual surveillance of the irradiated area for basaloid carcinoma in LFS carriers, in HNSCC particularly in the larynx, pharynx, and oral cavity (Guha and Malkin, 2017; Frebourg et al., 2020; Nosé and Lazar, 2022).

Fanconi anaemia (FA) is a rare autosomal recessive DNA repair disorder caused by biallelic inactivation of one out of the 21 causal FA genes described so far. All FA genes code for proteins associating in a multiprotein complex participating in the resolution of interstrand crosslinkings, a highly genotoxic DNA lesion (Che et al., 2017). At the cellular level, there is a high degree of genomic instability and an increased sensitivity to bifunctional alkylating agents. FA is characterized by congenital abnormalities, bone marrow failure, and predisposition to malignancies, in particular, acute myeloid leukaemia and squamous cell carcinoma (SCC; including HNSCC). Recently, the prevention and treatment of HNSCC in FA patients have received increased attention as the proportion of patients surviving to adulthood is rising (Alter et al., 2014; Dufour, 2017). Compared to the general population, the risk of HNSCC in FA is increased 500- to 800-fold, and the diagnosis of HNSCC often precedes the diagnosis of FA (Prime et al., 2001; Scheckenbach et al., 2012). The cumulative incidence of gynaecological SCCs and HNSCCs is 30 % at the age of 40 years (Alter et al., 2014; Dufour, 2017). Early detection allowing surgical therapy alone is the most appropriate approach because therapy with alkylating cytostatics and RT often leads to considerable toxicity. Therefore, to detect HNSCC early, screening oral examination every six months is recommended in patients with FA (Dufour and Pierri, 2022).

Familial atypical multiple mole melanoma syndrome (FAMMM) is caused by a specific inactivating GPV in the *CDKN2A* gene that encodes tumour suppressor proteins $p16^{INK4A}$ and $p14^{ARF}$, a potent inhibitor of CDK4/CDK6 activation at the transition of G1 restriction point (Chan et al., 2021; Mori, 2022). Although patients with *CDKN2A* GPV traditionally manifest with multiple mole melanoma (25–40 %), melanoma-pancreatic cancer syndrome (60 %), in association with CDKN2A mutations, a higher incidence of other tumours such as HNSCCs, neural tube tumours, gastrointestinal tract tumours, breast carcinoma, and lung adenocarcinoma has been reported (Cabanillas et al., 2013; Lynch et al., 2016; Jeong et al., 2022). While melanoma incidence is independent of mutation variants in p16INK4A and/or

p14ARF, variants affecting the $p16^{INK4A}$ transcript are observed more frequently in pancreatic cancer and HNSCCs (42 %) compared to $p14^{ARF}$ (28 %) (Chan et al., 2021). As a novel relation between CDKN2A/p16 copy number loss, Cdk2 activation, replication stress, and hypersensitivity of HNSCC cells to checkpoint kinase inhibitor (CKI) monotherapy was found, CDKN2A/p16 analysis may represent a potential biomarker for selecting HNSCC patients for CKI therapy in the future (Gadhikar et al., 2017).

The Bloom syndrome (BS) is an autosomal recessive genetic disorder caused by GPV in the *BLM* gene, which encodes the DNA repair enzyme RecQL3 helicase (Ababou, 2021). Without proper DNA repair mechanisms, abnormal DNA exchange takes place between sister chromatids and results in genetic instability that may lead to cancer. BS patients present with narrow facial features, elongated limbs, and various dermatological complications, including photosensitivity, poikiloderma, and telangiectatic erythema and are more common in the Ashkenazi Jewish population. BS is associated with the development of haematological malignancies or solid tumours in a wide variety of anatomical sites. Compared with the general population, where HNSCC incidence is approximately 6 %, the incidence of HNSCCs in BS patients was reported to be around 18 %, the most common sublocalizations being the larynx and the tongue (Berkower and Biller, 1988; Arora et al., 2014; Nosé and Lazar, 2022).

Dyskeratosis congenita (DC) occurs rarely and predominantly affects males. DC manifests clinically as the triad of reticular hyperpigmentation, nail dystrophy, and leukoplakia and is associated with an increased risk of malignancy and other serious disorders such as bone marrow failure, and lung and liver diseases. One-fifth of GPVs can be found in *DKC1*, the gene encoding dyskerin, but GPVs in the *TERT* gene are reported most frequently (AlSabbagh et al., 2020). HNSCC has been reported in various sites of the upper aerodigestive tract (most cases described occurred in the tongue) in DC patients with an early onset (Komune et al., 2010; Manfuso et al., 2021). The cumulative incidence of tumours in DC patients is 40–50 % by 50 years of age; the most common solid tumours were HNSCC (40 %) and carcinoma of the anus (Alter et al., 2009). The ratio of observed to expected (O/E ratio) cancer cases in the National Cancer Institute registry was 11-fold ($P < 0.05$) in patients with DC compared with the general population, with the most increased O/E ratio for the tongue cancer and acute myeloid leukaemia (Alter et al., 2009). Genotoxic treatments (RT, chemotherapy) are associated with a high risk of secondary malignancies and should be avoided (AlSabbagh, 2020).

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder caused by biallelic inactivation of one of the seven XP genes identified so far (Rizza et al., 2021). XP is characterized by nucleotide excision repair (NER) deficiency, a DNA repair pathway involved in DNA damage mainly caused by ultraviolet (UV) radiation. The XP complementation group C (XP-C) is one of the most common cases (Prime et al., 2001; Schärer, 2013, Leung et al., 2022; Nosé and Lazar, 2022). Compared to the general population, XP patients have a lifetime risk of non-melanoma and melanoma skin cancers that is approximately 10,000 and 2,000 times higher, respectively (Leung et al., 2022). Several case reports have documented early-onset HNSCCs in patients with XP, most commonly in the orbital region (90 %), on the lip or tongue (Sibar et al., 2016; Baykal et al., 2021; Leung et al., 2022). DNA-damaging treatment modalities (e.g., RT) and particularly cisplatin-based chemotherapy should be used with extreme caution, as they can cause serious and potentially fatal adverse events (Carneiro et al., 2020).

Familial clusters of HNSCCs

In contrast to the rare hereditary syndromes with clear Mendelian inheritance and often dramatic clinical manifestations described above, HNSCCs have also been shown to cluster in some families. A positive family history of HNSCC is associated with a 2- to 4-fold increased risk of HNSCC (Foulkes et al., 1995; Negri et al., 2009). The risk is up to 8-fold if the affected relative is a sibling rather than a parent (Foulkes et al., 1995), and for more distal anatomic sites of HNSCCs (hypopharynx and larynx). The risk is also higher or restricted to individuals exposed to tobacco (Negri et al., 2009).

The occurrence of second primary tumours in the upper aerodigestive tract is a common cause of treatment failure in HNSCC. Interestingly, Bongers et al. (1996) have shown that having one or more first-degree relatives with HNSCC is a risk factor for the development of a second primary tumour after initial HNSCC in smokers.

Clusters of familial nasopharyngeal carcinoma (NPC) have also been documented outside the typical geographic distribution (China, Southeast Asia) (Ung et al., 1999; Jia et al., 2004; Kara et al., 2022). Ung's report from Taiwan describes a more than 7-fold increased risk of NPC in patients with a first-degree relative with the same tumour, whereas those with a family history of another malignancy had only a slightly increased risk (Ung et al., 1999). A Chinese study by Ji et al. (2011) suggests that positive family history of this carcinoma leads to 12-fold increased risk of NPC and, together with cigarette smoking, contributes to the NPC risk. The association of NPC risk with cigarette smoking is stronger for non-keratinizing compared to keratinizing SCCs, whereas family history is strongly associated with keratinizing SCCs, a less common histological type. Family clustering suggests a genetic background of NPC, but no single causal gene has been clearly associated with HNSCC. Tanaka et al. (2012) have reported germline heterozygous missense variant c.6431A>G in the FAT domain of the *ATR* (ataxia telangiectasia and Rad3 related) gene in a Caucasian family (24 affected individuals in a 5-generation pedigree) with an oropharyngeal cancer and other mild abnormalities in the hair, teeth

and nails, along with skin telangiectasia. Furthermore, a susceptibility locus on chromosome 3p21 linked to familial NPC has been identified in the Chinese population, suggesting that the NPC susceptibility gene may be located in this chromosomal region (Zeng et al., 2006). The loss of heterozygosity in the 4p15.1-4q12 region in NPC patients with a positive family history suggests that another potential susceptibility gene locus may be present in 92 % of cases (Liu et al., 2007). In addition, familial NPC is associated with specific human leukocyte antigens (HLA) (Tse et al., 2009; Tang et al., 2012; Wang et al., 2018). Moreover, polygenic risk scores (PRS) might also have the potential to identify individuals at risk for disease (Hovhannisyan et al., 2023). Recently, a genome-wide association study (GWAS) has derived PRS for NPCs in China, using previously identified risk loci (3q26, 5p15, 6p21.3, 6p22.1, 9p21, 13q12) and six novel loci associated with the HLA system. In summary, the GWAS-derived PRS, together with the EBV test, can significantly improve the NPC risk stratification (He et al., 2022).

Germline genetic testing criteria in HNSCCs

Germline genetic testing criteria are usually designed to define a group of patients with a probability of detecting a causal GPV higher than 10 %. Unlike some other cancers such as breast, ovarian, or colorectal cancer with defined genetic testing criteria, routine germline genetic testing in HNSCCs is not currently recommended, as it is considered to be predominantly of sporadic origin and the frequency of GPVs in established cancer predisposition genes is anticipated to be low.

Currently, germline genetic testing in patients with HNSCCs may be considered (Negri et al., 2009; Bertonha et al., 2015; Birkeland et al., 2016) in the case of:

a) a minimum of two first-degree relatives affected by HNSCC and/or other related cancers (cancer of stomach, kidney, breast, uterus, cervix, etc.),
b) age < 45 years at onset in at least one of the affected family members,
c) HNSCC patient with no known aetiological factors such as tobacco or alcohol use, at any age of onset.

To date, there have been few reports on germline genetic testing in HNSCC. In 2018, a small Greek study involving 30 young patients with oral cavity HNSCCs, representing a selected cohort of non-drinkers, non-smokers, and HPV-negative patients to avoid the influence of common risk factors, found that 13.3 % of them carried a GPV in genes associated with various types of cancer, with *CDKN2A* being the most common (Fostira et al., 2018). These patients have higher risk of melanoma, pancreatic cancer, and even HNSCCs (Cabanillas et al., 2013). Another GPV was found in the *SDHB* gene that is associated with the paraganglioma or pheochromocytoma risk. However, no association with HNSCC has been demonstrated to date (Buffet et al., 2020). The third GPV in this study was in the *RECQL4* gene, whose biallelic GPVs cause the Rothmund-Thomson syndrome with an increased risk of osteosarcoma, but no association with HNSCCs has been demonstrated. Interestingly, somatic alterations of the *RECQL4* gene have been reported in oral HNSCCs (Van Kempen et al., 2015).

Cury et al. (2021) performed whole-exome sequencing in 45 HNSCC patients (including 35 tumours arising in the oral cavity and 10 oropharyngeal). They studied young patients (≤ 49 years), as their shorter exposure to the known risk factors may be insufficient to initiate HNSCC development and genetic susceptibility may be more pronounced. Most patients were male, smokers, and almost half were HPV positive. At least one GPV in DNA repair pathway genes was found in 67 % of cases, including GPVs in *CDKN2A* and *RECQL4* in HPV-negative patients with oral cancer and in *FANCG* in HPV-positive HNSCC patients (Chandrasekharappa et al., 2017).

Recently, Brake at al. (2023) published the results of a subset of unselected squamous and non-squamous head and neck carcinomas that were part of the INTERCEPT prospective cohort study. The group of head and neck carcinoma patients was larger than in previous studies and included 200 patients, but it was very heterogeneous with 75 % HNSCCs and other histological groups such as adenocarcinoma, neuroendocrine differentiated tumours, thyroid histologies, or salivary/secretory carcinoma. The median age of the studied cohort was 62 years, over two thirds were men, half of the patients were smokers, the HPV status was known in 75 % of them. In the HNSCC group, 15 GPVs were detected in 14 patients (10 % of HNSCC in the cohort) and included GPVs in *CDKN2A, RECQL4, BARD1, BRCA1, HOXB13, MITF, MUTYH, PSM2, RAD51D*, and *WRN*. The significance of these GPVs for the HNSCC development is not yet clear. Importantly, no GPV carriers met the germline genetic testing criteria.

Future directions

A significant proportion of patients with HNSCC appear to carry some GPV in a clinically significant cancer predisposition gene. So far, criteria for testing for only a few rare syndromes associated with head and neck carcinoma have been published, e.g., Multiple Endocrine Neoplasia (MEN) type II, but none of these syndromes are associated with HNSCCs. Understanding the significance of different GPVs in predisposing genes and determining the associated risks will allow individualized screening. In addition, identification of healthy GPV carriers will allow personalized recommendations for screening and cancer prevention in individuals at increased HNSCC risk. The identification of GPVs can also influence the therapy. Although most GPVs cannot be targeted now, precision-guided targeted antibodies and small molecule inhibitors promise to change this in the future. For example, the use of a cyclin-dependent kinase inhibitor may be a potential therapeutic approach for *CDKN2A* in HNSCC (Ahn et al., 2020) or other tumour-agnostic therapy options listed in Table 1.

Table 1. Tumour-agnostic therapy options for HNSCC patients based on the presence of germline pathogenic variants

Target	Treatment	Condition	Trial phase	NCT number
BRCA1/2	olaparib	ovarian cancer	3	NCT01874353 (Pujade-Lauraine et al., 2017)
		breast cancer	3	NCT02000622 (Robson et al., 2019)
		pancreatic cancer	3	NCT02184195 (Golan et al., 2019)
		prostate cancer	3	NCT02987543 (de Bono et al., 2020)
	olaparib + durvalumab + tremelimumab	homologous recombination repair gene-mutated cancer	2	NCT04169841 (Fumet et al., 2020)
MLH1, MSH2, MSH6, PMS2	pembrolizumab	microsatellite instability/ mismatch repair-deficient cancer	2	NCT02628067 (Marabelle et al., 2019)
CDKN2A	palbociclib + cetuximab	HNSCC	2	NCT02499120 (Adkins et al., 2019)
RET	vandetanib	medullary thyroid cancer	3	NCT00410761 (Wells et al., 2012)
	selpercatinib	RET-altered thyroid cancer	1–2	NCT03157128 (Wirth et al., 2020)

Conclusion

Based on the limited above-mentioned data, up to 10 % of HNSCC patients seem to carry at least one GPV in an established or candidate cancer predisposition gene. Hereditary syndromes with clinical manifestation of HNSCCs are rare but their clinical manifestation is dramatic. These syndromes often lead to cancer at a young age, even in the absence of traditional risk factors such as tobacco and alcohol use. In addition, next-generation sequencing has revealed a large number of GPVs in candidate predisposition genes, but their clinical significance is currently unknown. Nevertheless, these variants can influence treatment decisions and have the potential to be targeted with precision medicine in the future. Further research and international collaboration are needed to fully realize the potential of germline testing to improve patient care and outcomes for HNSCC patients.

Conflict of interest

All authors declare that they had no conflict of interest.

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