Published in final edited form as:

Curr Oncol Rep. 2023 April ; 25(4): 269–278. doi:10.1007/s11912-023-01364-x.

Translocations and gene fusions in sinonasal malignancies

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Abstract

Purpose of Review: During the past few years there has been an expansion in our understanding of gene fusions and translocations involved in cancer of the sinonasal tract. Here we review the downstream biologic effects, clinical characteristics, and pathologic features of these tumors. The molecular consequences and neo-antigens resulting from these chromosomal aberrations are considered and targets for current and future clinical trials discussed.

Recent Findings: Several new, clinically relevant, chromosomal aberrations have been discovered and evaluated to varying degrees in sinonasal tumors including DEK::AFF2, BRD4::NUT, ADCK4::NUMBL, and ETV6::NTRK3, among others.

Summary: Sinonasal malignancies demonstrate a diverse genetic landscape and varying clinical courses. Recent studies demonstrate that gene fusions and translocations may play a role in carcinogenesis in certain sinonasal tumor sub-types and may be used to develop new biomarker driven and patient-centered treatments.

Keywords

Translocation; Gene fusion; Sinonasal malignancies; Neo-antigen; Chimeric protein

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Conflicts of Interest

All other authors declare no competing interests.

Introduction

Sinonasal malignancies make up 3% to 5% [1, 2] of all head and neck cancers and are found in the nasal cavity as well as the maxillary, frontal, sphenoid, and ethmoid sinuses. They have a reported incidence of 0.556 [3] to 0.83 [1] per 100,000 persons per year and a male predilection of approximately 1.8:1 [1]. Within the broad classification of these tumors exists a wide variety of histological subtypes, the most common being sinonasal squamous cell carcinoma (SNSCC) making up about 50% of all sinonasal malignancies [4••]. Treatment is largely dependent on disease pathology, stage at presentation, and anatomical location but oftentimes includes surgical resection followed by adjuvant radiation therapy [5]. Given the rare nature of these tumors, multi-institutional efforts are necessary to make treatment advances and improve outcomes for these patients [6].

Acquired chromosomal abnormalities were postulated to play a role in carcinogenesis as early as 1914 [7]. However, due to technical limitations this idea could not be critically evaluated until over half a century later [8]. This culminated in the first specific translocation in human neoplasia confirmed in 1973 with the t(9;22)(q34;q11) Philadelphia Chromosome in chronic myelogenous leukemia [9]. Types and patterns of genetic aberrations are variable, ranging from ploidy shifts to single-base substitutions and epigenetic alterations [10–12]. Chromosomal rearrangements may lead to either dysregulation of gene expression through promoter insertion near a proto-oncogene or gene truncations where a negative regulatory site has been functionally inactivated [13]. Translocations may also lead to the creation of a new fusion gene, expressing a chimeric protein that may affect downstream signaling cascades or the regulation of cell division.

As therapies become increasingly driven by the molecular landscape of a patient's cancer, identification and characterization of chromosomal rearrangements for therapeutic application is paramount. Clinical trials have shifted from tumor type to gene or signaling pathway-directed, tailored to specific biomarkers. Early intervention with precision therapy has shown improved outcomes related to the elimination of residual disease and reducing treatment resistance [14]. Recently, new translocations and gene fusion proteins have been described in several subtypes of sinonasal cancer [15–18]. This article will review the effect of chromosomal translocations and gene fusions on malignancies of the nasal cavity and paranasal sinuses. We will touch on the molecular, histological, and clinical features of the fusions and translocations found in these cancers and discuss their potential relevance as targets for precision therapy.

DEK::AFF2 fusion-associated carcinoma: an emerging subtype of squamous cell carcinoma

This newly described subtype of head and neck cancer can occur in the nasal cavity, paranasal sinuses, skull base, orbit, and temporal bone [15, 19–22]. The human *DEK* gene is located on chromosome 6p22.3 and has notable roles in chromatin reorganization [23] as a proto-oncogene in a subset of acute myeloid leukemia [24]. The *AFF2* gene, located on the X chromosome (Xq28), is an RNA-binding protein that may play a role in alternative splicing and has been associated with Fragile X syndrome [25]. While the *DEK* breakpoint is reported at exon 7, multiple breakpoints in *AFF2* at exons 4, 6, and 9 have been described,

all of which are in-frame [15, 20•−22]. The resultant chimeric protein is thought to retain the function of both genes [19]. However, the oncogenic mechanisms of the DEK::AFF2 fusion protein have yet to be fully elucidated.

The frequency of *DEK::AFF2* is not yet clear; however, in one case series RNA sequencing demonstrated the *DEK::AFF2* fusion in 13 of 27 cases of non-keratinizing squamous cell carcinoma of the sinonasal cavity and skull base that were negative for the human papillomavirus (HPV) and the Epstein-Barr virus [20•]. The clinical course is varied, but these tumors often locally recur. The range of reported ages at diagnosis of *DEK::AFF2* carcinoma is as early as 18 years to as late as 79, with most of the malignancies occurring in females [20•]. Most described tumors occur in the nasal cavity or paranasal sinuses. The majority of these cancers have features of non-keratinizing squamous cell carcinoma, however foci of keratinization can be found [26]. Histologically, these tumors exhibit shared characteristics of mixed exophytic and endophytic growth with broad papillary fronds alternating with anastomosing lobules, ribbons, and nests, with peripheral palisading, and cellular monotony. In several case series and reports [19–21], the immunohistochemical phenotype included diffuse positivity for either p40 or p63. Interestingly, Schneiderian carcinoma can appear histologically similar to *DEK::AFF2* carcinoma and multiple samples in one case series had been previously misclassified as Schneiderian carcinoma [20•, 27–30].

The *DEK::AFF2* fusion was first discovered in a patient with metastatic head and neck cancer who had an exceptional and complete response to immune checkpoint blockade with pembrolizumab (anti-PD-1) [15]. Interestingly, this tumor had a relatively low tumor mutational burden and minimal immune cell infiltration, features that are commonly seen in tumors with a propensity for a poor response to immune checkpoint blockade. The group in this study further demonstrated that the *DEK::AFF2* in-frame translocation produced a neoantigen that could elicit a host cytotoxic T cell response [15]. This critical study highlights that genetic translocation events such as *DEK::AFF2* can kindle tumor-specific antigens rendering immunotherapeutic approaches a potential treatment strategy for these tumors.

Nuclear Protein in Testis (NUT) Carcinoma – *BRD4::NUT*

NUT carcinoma (NC) is a rare and aggressive malignancy that arises predominately in the thorax and head and neck. This malignancy consists of a chromosomal translocation of the *NUT* gene (*NUTM1*) on chromosome 15q14. About two-thirds of carcinogenic mutations include *NUT* fused with bromodomain-containing protein 4 (*BRD4*) on chromosome 19p13.1 [31, 32]. Other genetic alterations include pairs with *BRD3, NSD3, ZNF532, ZNF592*, or *CIC* [33, 34]. *BRD4::NUT* is associated with a poorer prognosis than non-*BRD4* fusions [35]. Studies have demonstrated NUTM1's role in activating telomerase reverse transcriptase (TERT) which promotes immortalization by protecting telomeres in cancer cells [36]. *BRD4* codes for a protein that on its own recognizes and binds acetylated histones and plays a key role in transmission of epigenetic memory across cell divisions and transcription regulation [37–39]. It has been demonstrated that the BRD4::NUT fusion protein disrupts squamous cell differentiation and promotes oncogenesis [40].

The clinical course of sinonasal NC is aggressive with early metastasis [31, 41]. Many patients present with symptoms of mass effect and in almost all reported cases patients died within 18 months. Autopsy of two patients showed extensive visceral organ metastasis [42]. Prior to discovery of underlying NUT translocations, this tumor was often previously classified as sinonasal undifferentiated carcinoma (SNUC) [43, 44]. Histological characteristics of the tumors include scant amounts of pale cytoplasm with a high nuclear to cytoplasmic ratio and abundant mitoses. The cells contained granular to vesicular chromatin in their nuclei that have one or more prominent nucleoli. Furthermore, cells are arranged in sheets, nests, and cords with zones of necrosis [45–49]. Immunohistochemical analysis of tumors involving the mutation showed positivity for p40 and p63, consistent with a squamous phenotype as well as positivity for MYC, a well described proto-oncogene [42, 46]. Interestingly, in tissue samples that contained both zones of differentiation and undifferentiation, NUT positivity was only seen in the undifferentiated areas. No cases showed any evidence of human papilloma virus or Epstein Barr virus infection [50].

Bromodomain Extra Terminal (BET) small molecule inhibitors target and bind the BRDT, BRD2, BRD3, and BRD4 proteins and have shown to slow proliferation and demonstrate squamous cell differentiation, potentially through regulation of MYC, in murine xenograft models [51, 52]. NUT carcinoma cell lines from a sinonasal primary site have recently been described as well as sensitivity to bromodomain inhibition [53]. Other initial pre-clinical studies have suggested that BET inhibitors may need to be combined with other anti-cancer agents to achieve maximum therapeutic benefit [52]. Clinical trials for NC, specifically, are currently underway and include NCT05019716 and NCT05372640, both of which are testing the safety and efficacy of a BET inhibitor – the former in combination with chemotherapy and the latter in combination with abemaciclib a selective CDK4/6 inhibitor.

Sinonasal Melanoma – *ADCK4::NUMBL*

Mucosal melanoma of the sinonasal tract (SMM) accounts for 0.3–2% of all melanomas and 4% of sinonasal tumors [4••, 54]. Gene fusions in this disease are rare but include *ADCK4::NUMBL, DCAF7::PRKCA, TERT::CNOT4, TERT::NUP50* [16], *FGFR3::TACC3* [55], and *EML4K::ALK* [56]. The most common of these is *ADCK4::NUMBL*, which was found as a fusion transcript in eight of 40 explored tumors of SMM [16]. The *ADCK4* gene codes for a protein involved in the biosynthesis of coenzyme Q [57] and the *NUMBL* gene codes for a developmental protein vital for neurogenesis [58, 59]. This fusion was functionally evaluated in cutaneous squamous cell carcinoma where it was thought it may promote proliferation of tumor cells [60]. Ultimately, however, its role in sinonasal melanoma is unknown.

SMM is an aggressive tumor that usually presents at an advanced stage and has a 25–30% 5-year survival rate [16]. Further research is needed to determine whether the presence of fusion transcripts have any effect on SMM disease severity. Histologically for non-fusion sinonasal melanoma, there are many possible phenotypes including but not limited to an epithelioid, spindle cell, round cell, or undifferentiated morphology. In these tumors a lack of pigmented melanin is common and immunohistochemical presence of melanocytic biomarkers is necessary for diagnosis [16, 54].

Potential therapeutic targets related to *ADCK4::NUMBL* are difficult to hypothesize without further functional studies elucidating the downstream signaling consequences of the fusion. The FGFR3::TACC3, previously associated with glioblastoma and other solid tumor malignancies, fusion protein is already used as a target for therapeutics through fibroblast growth factor receptor inhibitors [55]. There is an important need for new treatment strategies in sinonasal melanoma given its aggressive nature and tendency to recur early. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibodies in combination with a PD-1 inhibitor has had some success in treating sinonasal melanoma but more investigation is warranted [61].

Sinonasal undifferentiated carcinoma (SNUC) – *PGAP3::SRPK1*

This rare undifferentiated, high-grade, carcinoma is a malignancy derived from the epithelium of the sinonasal tract. SNUC is aggressive with a predilection for early invasion and distant metastasis [62]. On histology it exhibits large undifferentiated cells with medium to large hyperchromatic and pleomorphic nuclei, and absence of squamous or glandular areas. This diagnosis represents a heterogeneous group of tumors classified by diagnosis of exclusion. SNUC remains a devastating diagnosis, however, recent shifts have occurred in the management of SNUC with a shift towards induction chemotherapy approaches [62, 63]. More investigation is warranted as certain tumors show an excellent response to induction chemotherapy while others are relatively resistant. New mutations have been identified in SNUC including isocitrate dehydrogenase-2 (IDH2) and SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) leading to new sub-categorization. However, it is not yet clear if these mutations or others are related to response to induction chemotherapy.

A recent study identified a *PGAP3::SRPK1* fusion gene via end RNA sequencing in a well described cell line derived from a patient with SNUC [17•, 64]. It was predicted that the novel fusion protein retains the protein kinase domain of SRPK1. Post-glycosylphosphatidylinositol (GPI) attachment to proteins factor 3 (PGAP3) is involved in GPI-anchor biosynthesis [65] while SRSF protein kinase 1 (SRPK1) plays a role in the regulation of gene splicing [66]. Furthermore, SRPK1 has been previously associated with gastric and colorectal cancers – driving proliferation, migration, and tumor invasion [67, 68]. Heft Neal et al. proposed this novel fusion protein plays a role in expression of CCND1, FOXO4, HSDL2, and NAGK. RNA sequencing analysis from *in vitro* assays using their studied SNUC cell line suggested the fusion has an important role in the EGFR, E2F, and MYC signaling pathways [17•].

ETV6 linked fusions in low grade sinonasal adenocarcinomas

Low grade sinonasal adenocarcinomas with ETV6 fusions have been previously grouped under secretory carcinomas. However, Andreasen et al. terms them with the novel classification *ETV6*-rearranged low-grade sinonasal adenocarcinoma (SNAC) citing histological and morphological differences [18, 69, 70]. In the initial study characterizing this distinct subset, an index case was identified and then 46 additional non-salivary and non-intestinal type low grade SNACs were tested for the rearranged *ETV6* gene of which 8.7% (4/46) were positive [69]. ETV6 is a transcriptional repressor that plays a role in

hematopoiesis and has shown to be involved in malignant transformation in hematological cancers [71]. ETV6 is often paired with NT-3 growth factor receptor (NTRK3) a receptor tyrosine kinase involved in the control of cell survival and differentiation [72]. Other fusion partners of *ETV6* include a single case of an *ETV6::RET* fusion, *RET* the well-studied proto-oncogene, which shares a phenotypic profile with *ETV6::NTRK3* [18]. An additional example is a single case of *ETV6::TNFRSF8* that was found in the sphenoid sinus of a 66-year-old male which demonstrated p63 positivity and was negative for presence of p16 and Epstein Barr Virus [73]. Tumor necrosis factor receptor superfamily member 8 (TNFRSF8) plays a role in the regulation of cellular growth and transformation as well as regulates gene expression through nuclear factor kappa B (NF-κB) [74, 75]. Based on data from analysis of hematologic malignancies, ETV6 mutants demonstrate increased cytoplasmic localization of its encoded repressor and are therefore deficient in transcriptional regulation. When paired with TNFRSF8, the oncogenic mechanism could be rooted in the incorrect localization of CD30 resulting in downstream effects on the NF-kappa-B, MAP kinase, and Akt signaling pathways [76]. Or when paired with NTRK3, unregulated cell survival and cellular differentiation. Functional studies of these potential mechanisms are warranted.

SNACs have clinical outcomes that tend to be fair when low grade and common presentations include a combination of epistaxis and nasal obstruction. The fusion positive tumors histological profile is composed of cylindrical cells and PAS+D positive granules in the apical cytoplasm [69]. Immunohistochemically, DOG-1 and S-100 positivity and lack of mammaglobin is characteristic of this disease [69]. Clinical trials are under way, NCT02637687 and NCT02576431, for solid tumors containing the NTRK fusion. The drug in question blocks the actions of NTRK genes and could a therapeutic option for future patients with *ETV6::NTRK3* fusions.

Biphenotypic Sinonasal Sarcoma (BSNS) – *PAX3::MAML3*

Sarcomas only account for 1–3% of all head and neck malignancies and BSNS is a low-grade spindle cell sarcoma with both neural and myogenic features that is locally aggressive [77]. These tumors are characterized by *PAX3* rearrangements usually paired with *MAML3*, other common fusion genes include *FOXO1*, *NCOA1*, *NCOA2*, and *WWTR1* [78]. Paired box protein 3 is a transcription factor that is involved in neural tube development and myogenesis [79] and has been associated with several different cancers as a potential oncogene. PAX3 is typically downregulated when muscle begins to differentiate, then muscle-specific transcription factors are activated. Untimely expression of PAX3 prevents myogenic differentiation prevents myoblasts from becoming myotubules. Also, when PAX3 is activated c-MET, a tyrosine kinase receptor, is upregulated pointing to a potential role for uncontrolled c-MET activation in tumorigenesis [80] while mastermind-like protein 3 (MAML3) is a transcriptional coactivator for NOTCH proteins, which are a group of proteins involved in cell-to-cell communication and regulate cell-fate determinations [81]. Recently, there was a case report that describes a *RREB1::MKL2* fusion, an alteration usually found in ectomesenchymal chondromyxoid tumors, in a 73-year-old patient with a maxilla-ethmoidal tumor that has the same immunohistochemical profile as BSNS including positivity for smooth muscle actin and S100 and showed focal positivity for β-catenin [82].

Also, reported in the literature was an oropharyngeal sarcoma with the same fusion [83]. More study is needed to determine molecular consequences of these fusions in BSNS.

The most common presenting symptoms of BSNS are related to mass effect like congestion, pain, epistaxis, rhinorrhea, or sinusitis [84]. Histologically, the tumors consist of hypercellular proliferations of monotonous spindle cells [85]. Features of high-grade cancer are typically absent, notably the lack of necrotic zones and only few mitotic figures. Immunohistochemically, cells are usually positive for smooth muscle markers, SMA or calponin, and are positive for S-100 and ß-catenin while consistently negative for SOX10. [84–87] Moreover, therapeutic options for BSNS may lie in targeting the c-MET pathway. MET inhibitors have shown some promise in treating non-small cell lung cancer and hepatocellular carcinomas. [88, 89] However, the results of multiple clinical trials indicate that these therapies need biomarker-driven patient selection to be a viable treatment.

Adenoid Cystic Carcinoma (ACC) of the Sinonasal Tract – MYB::NFIB

ACC is an uncommon malignancy that occurs typically in the major and minor salivary glands but can also occur in other tissues that contain secretory glands like the sinonasal tract [90, 91]. The MYB::NFIB fusion protein is characteristically overexpressed in these tumors. In a study of 61 ACC of various sites, seven from the nasal cavity, the *MYB::NFIB* fusion was found in 39 specimens, positive in five of the sinonasal tumors [92]. This fusion protein is caused by a balanced translocation t(6;9)(q22–23;p23–24). *MYB* codes for a transcriptional activator that plays a central role in the control of cellular proliferation and *NFIB* codes for a transcriptional activator of GFAP [93]. The *MYB::NFIB* fusion transcript explored by Brill et al. [92] suggests that the protein retains the DNA-binding and transactivation domains of wild type MYB with the negatively regulating microRNA binding domain replaced with the NFIB protein and therefore is expected to activate downstream MYB target genes in an unregulated fashion.

Sinonasal ACC is characterized by insidious growth and perineural invasion with intracranial extension [90]. This neoplasm occurs equally in both men and women and does not favor a particular age group. These tumors are typically slow growing but frequently metastasize and have poor long-term survival [92]. On histology, sinonasal ACC is a biphasic tumor of ductal and myoepithelial cells and the architecture has patterns that are cribriform, tubular, and solid. Immunohistochemically the tumors demonstrate positivity for p63, S-100, SMA, and cytokeratin [94, 95].

Pre-clinical studies have been done to assess *MYB*'s potential as a target for precision therapy and have shown promising results [96]. A subsequent clinical trial, NCT03287427, is studying the efficacy of a DNA vaccine constructed by an inactivated *MYB* gene with the universal tetanus T cell epitope on either side in combination with the anti-PD-1 antibody Tislelizumab in cancers where *MYB* is implicated.

Solitary Fibrous Tumors (SFTs) – *NAB2::STAT6*

The *NAB2::STAT6* fusion is used diagnostically as a marker for SFTs, which are a fibroblastic neoplasm that most often affects adults in their 5th or 6th decade of life and can arise in multiple locations throughout the body including the sinonasal tract [97, 98].

The human *NAB2* gene's function has not been explored at the protein level but is thought to act as a transcriptional repressor for zinc finger transcription factors based on sequence similarity [99], whereas the signal transducer and activator of transcription 6 (STAT6) protein is involved in interleukin-4 and interleukin-3 mediated signaling [100]. When the fusion protein was explored by Park et al. they demonstrated that cell lines transfected with the *NAB2::STAT6* fusion gene had increased cellular proliferation and migration of fibroblasts [101]. Histologically, SFTs demonstrate hypocellular and hypercellular areas composed of spindled to ovoid tumor cells with scant cytoplasm and indistinct cell borders, in an architecture with no discernible pattern. However, phenotype and morphology tend to be extremely broad for this type of neoplasm [102, 103].

Stevens et al. described two cases of Teratocarcinosarcoma (TCS)-Like neoplasms occurring in the nasal cavity harboring the *NAB2::STAT6* fusion which dramatically differ in their immunoexpression from SFTs [102]. They were biphasic tumors with a spindle cell neoplasm with mixed primitive neuroepithelial and carcinomatous elements thus also meeting criteria for TCS [102, 103]. Two cases of Adamantinoma-Like head and neck tumors harboring the *NAB2::STAT6* fusion which also differed histologically from SFTs were described, perhaps pointing to the potential for a broader *NAB2::STAT6* class of neoplasms than previously thought [102].

For SFTs the traditional treatment is multimodality therapy with primary surgical resection and outcomes are generally fair with a 5 year survival rate of 59–100% [97]. However, i*n vitro* studies demonstrate that IGF2 expression is induced in cells expressing the NAB2::STAT6 protein. As increased IGF2 expression is known to be associated with cancer via the PI3K/Akt signaling pathway IGF2 inhibitors may be a potential treatment to evaluate for SFTs and this new class of TCS-Like neoplasms [101, 104].

Discussion

Translocations and gene fusions in sinonasal malignancies are an active area of investigation. Table 1 presents additional fusions and translocations found in tumors arising in the nasal cavity and paranasal sinuses described in a case report or small case series, it also includes the *CHD4::AFF2* fusion which is of interest when considered with the *DEK:AFF2* fusion gene. The growing number of identified genetic alterations points to their potential foundational role in some sinonasal malignancies. Further investigation is needed to explore the neoplasm features mentioned in Table 1 for future therapeutic applications. Moreover, chromosomal translocations can be identified, if the translocation is known and described, by conventional and spectral karyotyping, fluorescence *in situ* hybridization (FISH), whole genome and RNA sequencing (WGS and RNAseq respectively), and by PCR. Immunohistochemistry can aid detection in specific cases, for instance NUT1 in NC, cMYB in ACC, and STAT6 in SFTs. Coordinated multi-institutional trials are warranted to better study their prevalence and to develop new diagnostic tools.

The downstream molecular consequences of chromosomal translocation in cancer can be due to deregulation of gene expression, inactivation of gene expression, or expression of a chimeric protein. The reason that all described cases in this review concern chimeric

proteins is potentially due to the RNAseq detection method as it exclusively works with the coding parts of a gene. It may well be that WGS, sparingly applied on sinonasal tumors, will reveal translocations that cause gene deregulation or inactivation. When considering therapeutic options in all cases of translocation or gene fusions, including those yet to be discovered, chimeric proteins may be specifically targeted for drug design or represent a neoantigen of interest with immunotherapeutic approaches or cancer vaccines. Signaling pathways of all types altered by translocations can also serve as targets for small molecule inhibitors.

Conclusions

This review demonstrates the growing importance of molecular characterization of translocations and gene fusions in sinonasal tumors. Clinical behavior of tumors with translocations is variable, NC and *DEK::AFF2*-associated carcinoma can be aggressive or locally recurrent whereas ETV6-rearranged low grade sinonasal adenocarcinoma are well differentiated with relatively fair outcomes. Moreover, only further molecular studies can explain why some translocations have a sub-site predilection while other tumors like those containing *ETV6::NTRK3* can occur throughout the body. Clinical trials are underway that target some of the same genetic alterations as the ones described here. With continued research and the expanded availability sequencing techniques more gene fusions and translocations will be identified which will hopefully lead to an increase in biomarker-driven clinical trials.

Funding

This research was supported (in part) by the Intramural Research Program of the NIH, NCI. This research was made possible through the NIH Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and contributions to the NIH from the Doris Duke Charitable Foundation (DDCF Grant #2014194), the American Association for Dental Research, the Colgate-Palmolive Company, Genentech, Elsevier, and other private donors.

N. London receives research funding from Merck Sharp & Dohme, LLC regarding HPV-related sinonasal carcinomas and holds stock in Navigen Pharmaceuticals, none of which are relevant to the present manuscript.

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Table 1.

More translocations and gene fusion found in literature

Translocation	Type of Tumor	Tumor Location	Neoplasm features	Citation
CHD4::AFF2	Neuroendocrine	Cervical lymph node metastasis from unknown primary	Non-keratinizing SCC similar to tumors containing the DEK::AFF2 Fusion	Miller et al. [105]
SYN2::PPARG	Low-grade non-intestinal type adenocarcinoma	Nasal Cavity	Aberrant CDX2 expression	Soon et al. [106]
EWSR1::ATF1	Hyalinizing clear cell carcinoma	Two cases occurring in the maxillary sinus, one case in the posterior ethmoid/ maxillary junction	Low-grade salivary gland tumors with different immunologic profiles	Lan et al. [107] AlAli et al. [108]
EWS::WT1	Desmoplastic Small Round Cell Tumor	Nasal Cavity	Rare malignancy that usually only occurs in the peritoneum, t(11;22)(p13;q12)	Lopez et al. [109]
CIITA::BCOR	Sarcoma	Nasal Cavity	Distinct family of sarcomas that occur throughout the body including the visceral organs	Yoshida et al. [110]
NONO::TFE3	(Perivascular epithelioid cell neoplasms) PEComa	Surface of the inferior turbinate	Normal sinonasal mucosa infiltrated by melanocytic proliferation	McGregor et al. [111]