The convergent roles of the nuclear factor I transcription factors in development and cancer

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Highlights

- NFI transcription factors play important roles in normal development and are associated with cancer in multiple organ systems.
- NFI transcription factors are implicated in tumours that arise from cells that normally express the concordant transcription factor during development.
- The role of NFI transcription factors in regulating the balance between cell proliferation and differentiation during development may be disrupted in cancer.
- NFI transcription factors are context-dependent in various cancer types and can play either oncogenic or tumour-suppressive roles.

Abstract

The nuclear factor I (NFI) transcription factors play important roles during normal development and have been associated with developmental abnormalities in humans. All four family members, NFIA, NFIB, NFIC and NFIX, have a homologous DNA binding domain and function by regulating cell proliferation and differentiation via the transcriptional control of their target genes. More recently, *NFI* genes have also been implicated in cancer based on genomic analyses and studies of animal models in a variety of tumours across multiple organ systems. However, the association between their functions in development and in cancer is not well described. In this review, we summarise the evidence suggesting a converging role for the *NFI* genes in development and cancer. Our review includes all cancer types in which the *NFI* genes are implicated, focusing predominantly on studies demonstrating their oncogenic or tumour-suppressive potential. We conclude by presenting the challenges impeding our understanding of NFI function in cancer biology, and demonstrate how a developmental perspective may contribute towards overcoming such hurdles.

Keywords

Nuclear factor one, Nuclear factor I, NFI, transcription factor, development, tumorigenesis

1. Introduction

Cancer is driven by a series of acquired features that facilitate the initiation and progression of tumorigenesis by deregulating cellular proliferation and differentiation [1]. These features are acquired as a consequence of changes in gene expression, compromising physiological pathways that are normally regulated to ensure the function and maintenance of mature cellular phenotypes and optimal organ system performance. Not surprisingly, many pathways that are mis-regulated in cancer also function during normal development to control the rapid growth and development of each organ system [2]. Normal biological processes important for development, such as cellular proliferation, differentiation, and migration, are often compromised in cancer. As such, transcription factors that normally regulate these processes in development are often disrupted during tumorigenesis, either by direct mutation, or indirectly through chromosomal translocation. The pathways regulated by these transcription factors can be associated either with paediatric tumours during development or with adult cancers which result from mutations that revert mature cells to a developmental phenotype that enables rapid proliferation. In the last decade, genomic analyses and studies in mouse models have implicated such transcription factors in a variety of tumours across multiple organ systems.

The NFI, or CCAAT box-binding transcription factor (CTF), family of genes was first described for its role in stimulating the initiation of adenovirus DNA replication. It was later found to play important roles in transcriptional regulation, particularly during development [3]. The NFI family consists of four transcription factors in humans and most vertebrates: NFIA, NFIB, NFIC, and NFIX [4]. These share a highly conserved DNA-binding domain at their N-termini, and therefore bind to a common DNA sequence

[5, 6] (Fig. 1). The C-termini of the NFI protein family demonstrate greater divergence, which is further compounded by the existence of multiple splice sites [7-11] and post-translational modifications [12-16]. Consequently, each NFI transcription factor encodes multiple splice variants, although the functions of many of these remain unknown.

NFI transcription factors regulate cell proliferation and differentiation during the development of multiple organ systems, including the central nervous system (CNS) [17-23], mammary gland [24], and lungs [18, 25] (Fig. 2). These transcription factors are also required to drive hematopoiesis [26-31], osteoblastosis [32-34] and melanocytosis [35, 36] (Fig. 2). However, NFI deregulation can lead to uncontrolled cell proliferation or a failure to differentiate, and could therefore potentially contribute to tumour growth. In this review, we describe the oncogenic and tumour-suppressive potential of the NFI transcription factors and discuss what is known about the function of these genes in various types of cancer, in the context of their function in these same organ systems during development (Fig. 2).

2. Central Nervous System Tumours

2.1 Glioma

In astrocytomas, high expression levels of *NFIA* [37] and *NFIB* [38] correlate with better clinical outcome (Table 1). For example, a high level of *NFIA* mRNA in adult grade IV glioblastoma (GBM) and paediatric grade III-IV astrocytomas is associated with improved survival [37] (Table 1). Similarly, high *NFIB* expression correlates with better overall survival probability in GBM, grade II-IV astrocytomas, and gliomas in general

[38] (Table 1). Higher-grade tumours are associated with lower *NFIA* [37] and *NFIB* [38] mRNA expression levels (Table 1). The percentage of cells that express NFIA protein, as detected by immunohistochemistry, is also reduced in higher-grade astrocytomas [37] (Table 1). These findings suggest that NFIA and NFIB function as tumour suppressors. This is corroborated by the identification of insertions that affect the NFI transcription factors in multiple insertional mutagenesis mouse models designed to identify genes involved in glioma tumorigenesis [39-41] (Table 2a). Notably, insertions within *Nfic* and *Nfix* have also been identified in these mouse models [41] (Table 2a), suggesting that NFIC and NFIX may also function as tumour suppressors in glioma.

Genomic aberrations affecting *NFIB* are observed in approximately 40% of human astrocytomas, mainly as loss of heterozygosity (LOH) due to large deletions of chromosome 9p, which harbours other tumour suppressors such as *CDKN2A* [42-46]. Furthermore, *NFIB* overexpression induces cell differentiation and inhibits growth in GBM tumours, an outcome which is mediated by STAT3 signalling [38]. This implies that *NFIB* functions as an essential driver of glial differentiation in glioma. Its disruption results in the failure of tumour cells to differentiate, inevitably contributing to sustained cell proliferation. This scenario reflects NFI function in the developing brain, where disruption of *Nfia*, *Nfib, and Nfix* results in reduced and delayed differentiation of glial cells, causing progenitor cells to remain in a proliferative state [17-23]. During prenatal development, NFIA and NFIB are expressed within neural progenitor cells that give rise to various glial and neuronal cell populations throughout the brain and spinal cord [47-49]. The high expression of these genes persists in both progenitor and differentiated cells of the adult brain, although their function in this case remains unknown [50].

Nevertheless, their reduced expression in high-grade gliomas suggests that disruption of NFI activity is important in gliomagenesis [37, 38] (Table 1).

Besides its potential role as a tumour suppressor, NFIA is also likely to act as a glioma type determinant. The percentage of NFIA-expressing cells in oligodendroglioma samples is consistently lower than in astrocytoma [37] (Table 1). Within the mRNA expression data of mixed glioma samples, low *NFIA* expression is associated with oligodendrogliomas and the enrichment of oligodendrocytic genes [51] (Table 1). Loss of *NFIA* as part of chromosome 1p31 also correlates with oligodendroglioma [52-54]. Furthermore, NFIA overexpression in a mouse model of oligodendroglioma resulted in tumours that resemble astrocytoma, suggesting a direct role for NFIA in regulating glioma subtype specificity [55].

The role of NFIA as a cell fate determinant appears to be conserved during CNS development. For instance, down-regulation of *NFIA* favours the oligodendroglial lineage in the developing spinal cord [55]. In addition, both NFIA and NFIB play an essential role in generating astrocytes from human fibroblasts *in vitro* [56]. Interestingly, NFIA expression appears to be required for the later stages of oligodendroglial differentiation during postnatal brain development [57]. In the adult neocortex, NFIA is more highly expressed in oligodendroglia than NFIB and NFIX, suggesting a role in maintaining oligodendroglial differentiation [50]. Therefore, while NFIA and NFIB have a tumour-suppressor role in astrocytoma, loss of NFIA could potentially contribute to oligodendroglioma in two ways, first as a glioma type determinant, and secondly by enhancing oligodendroglioma growth.

2.2 Medulloblastoma

Various mouse models have demonstrated that loss of *NFI* also contributes to tumour initiation and progression in medulloblastoma. The *Nfi* loci have been identified as common insertion sites in insertional mutagenesis mouse models of medulloblastomas of the Sonic Hedgehog (SHH) subgroup [58-60] (Table 2a). Since many of these insertions are shared between the primary tumour and metastases, it is likely that insertions within the *Nfi* loci represent early events that contribute to tumorigenesis or tumour progression [60]. This role has been corroborated in a mouse model of SHH medulloblastoma with heterozygous loss of *Nfia* [58] (Table 2a). In these mice, reduced *Nfia* expression results in higher tumour incidence and decreased tumour latency [58]. These findings suggest that NFIA acts as a tumour suppressor of SHH-medulloblastoma.

The role of *Nfi* in the postmitotic differentiation of cerebellar granule neurons (CGNs), the cell type that gives rise to SHH-medulloblastomas [61], has been extensively studied [62-65]. During postnatal cerebellar neurogenesis, mature CGNs within the internal granule cell layer (IGL) strongly express the NFI transcription factors, including NFIA and NFIB [62, 66]. *Nfia* deletion in mice disrupts postmitotic CGN differentiation within the IGL [62, 64]. Thus, the defective differentiation of CGNs due to the loss of NFIA could contribute to the initiation of SHH-medulloblastoma [58] (Table 2a). Although the role of NFIB in postmitotic CGN differentiation has not been investigated as *Nfib* knockout mice die perinatally, defects in CGN development were reported at embryonic day 18 [18]. Given that *NFIB* expression is elevated in mature CGNs [62], it is likely that loss of *NFIB* also contributes to the initiation of SHH-medulloblastoma. It should be noted, however, that the role of NFI in medulloblastoma could be molecular context-

dependent. No *Nfi* insertions were reported in another insertional mutagenesis mouse model with *Tp53* deletion [60]. Overall, the role of the NFI transcription factors in medulloblastoma highly correlates with their role in development. These findings suggest that further study of the *NFI* genes and the pathways that they regulate during cerebellar and hindbrain development may be useful for understanding and treating these tumour types.

3.0 Carcinomas

3.1 Adenoid cystic carcinoma

The NFI transcription factors, particularly NFIB, appear to play a prominent role in various carcinomas, including adenoid cystic carcinoma (AdCC), breast carcinoma, and lung carcinoma (Table 3). In AdCC, *MYB-NFIB* fusion, or a similar fusion event affecting the *MYB* homologue, *MYBL1,* is found in 50% of tumours [67-76] (Table 3). This frequent fusion event is regarded as a molecular hallmark of AdCC [70, 75, 77]. Interestingly, this event always involves *MYB* fusing to the 3' end of the *NFIB* locus, suggesting that preservation of this region is critical for AdCC tumorigenesis [68, 69, 73]. Indeed, it was recently reported that this fusion event allows *NFIB* enhancers to drive *MYB* expression, thereby establishing a positive feedback loop that sustains expression of the oncogenic MYB protein [78].

Although increased expression of *MYB* or *MYBL1* is crucial to AdCC tumorigenesis, NFIB is likely to play an independent role as a tumour suppressor. All reported *MYB-NFIB* translocations disrupt the *NFIB* coding sequence [68, 69, 73] and independent

fusion events between *NFIB* and other fusion partners have been reported [70, 79-81] (Table 3). Moreover, the detection of truncating mutations and homozygous deletion of *NFIB* have also been identified in AdCC [70, 75, 78, 82]. These findings warrant further investigation of NFIB function in AdCC, particularly in cases where *MYB* or *MYBL1* expression is unaffected.

Although the role of NFIB in salivary gland development has not been well studied, *Nfib* knockout mice display defects in terminal tubule formation and tubule cell differentiation during submandibular gland development [83]. Given that AdCC arises from epithelial cells of the secretory glands, most commonly the salivary glands of the head and neck [84], understanding the role of NFIB in salivary gland development could contribute to our understanding of how its loss is involved in AdCC. We speculate that the disruption of NFIB caused by the *MYB-NFIB* translocation perturbs epithelial cell differentiation, maintaining the proliferative state of these cells and thereby promoting AdCC tumorigenesis.

3.2 Lung carcinoma

In contrast to its potential tumour suppressor role in AdCC, NFIB appears to promote tumorigenesis in small cell lung cancer (SCLC). High expression or amplification of *NFIB* has been reported in both human and mouse primary SCLC tumours and cell lines, suggesting that NFIB functions as an oncogene in this tumour type [85, 86] (Table 1). Indeed, overexpression of NFIB promotes tumour initiation and metastatic progression in mouse models of SCLC *in vivo* [87-89] (Table 2b and 2c). One underlying mechanism

involves NFIB binding to chromatin and increasing its accessibility at distal regulatory elements that regulate pro-metastatic protein expression [87]. *NFIB* expression is also associated with increased cell proliferation in SCLC cell lines *in vitro* [85], whereas its knockdown induces the opposite phenotypes: reduced proliferation, and increased apoptosis and senescence [85, 89].

The role of NFIB as an oncogene in lung carcinoma appears restricted to SCLC. In squamous cell carcinoma, no correlation was observed between *NFIB* expression and clinical outcome [90], while NFIB down-regulation is associated with poor clinical outcome and increased aggressiveness in non-small cell lung carcinoma (NSCLC) (Table 1). Contrary to its role as a pro-metastatic oncogene in SCLC, *NFIB* is down-regulated during epithelial-to-mesenchymal transition (EMT) in a NSCLC cell line *in vitro* [91]. Coincidentally, mesenchymal-to-epithelial transition (MET), a process that normally occurs during lung development, is disrupted in the lungs of *Nfib*-deficient mice [18]. Specifically, the differentiation of type I and II epithelial cells is defective and the lung mesenchyme is thickened due to the increased number of mesenchymal cells [18]. Defective MET resulted in defects in lung maturation, causing *Nfib*-deficient mice to die at birth [18, 25]. These findings suggest that NFIB is essential for driving mesenchymal-to-epithelial differentiation during lung development, and that it may also be required for epithelial cell maintenance following development. Consequently, loss of NFIB may play a role in the EMT of differentiated epithelial cells and epithelial stem cells in NSCLC [92], contributing to the development of these tumours. As SCLC arises from lung neuroendocrine cells [93], further studies are required to determine whether NFIB is required for the development of these cells, and how this process is maladapted in SCLC.

3.3 Breast carcinoma

Overexpression or amplification of *NFIB* is a common feature of oestrogen receptor (ER)-negative breast carcinoma [94-98] (Table 1). Microarray analyses have demonstrated that *NFIB* expression is a predictor of extensive residual disease following taxane-anthracycline chemotherapy in ER-negative breast cancer [99]. As such, NFIB expression may be associated with cancer aggressiveness in this tumour type, with *NFIB* knockdown *in vitro* being shown to reduce proliferation in ER-negative breast cancer cells [95], demonstrating its oncogenic potential. NFIC, on the other hand, may function as a tumour suppressor in breast carcinomas. Overexpression of the NFI-C2 isoform in an ER-negative breast cancer cell line inhibits cell proliferation and tumour growth [9]. A similar observation has been reported for NFIC in ER-positive breast cancer cells, in which *NFIC* knockdown resulted in increased proliferation and the expression of the CCND1 oncogene [100]. Thus, NFIB may function as an oncogene in ER-negative breast cancer, whereas NFIC functions as a tumour suppressor in both ER-positive and ER-negative breast cancers.

NFIB and NFIC play essential roles in various stages of mammary gland development [24]. These transcription factors are highly expressed in terminally differentiated mammary epithelial cells during mammary gland development [8, 101], and are involved in the transcriptional regulation of mammary-specific proteins [14, 101-111]. Deletion of *Nfib* from mammary stem cells and differentiating alveoli, however, appears to have little or no impact on cell differentiation in the mammary gland [112], indicating that NFIB may be redundant for epithelial cell differentiation. NFI-C2 expression in epithelial cells decreases at lactation and is restored at involution [113], suggesting that NFI-C2 could be

required for epithelial cell differentiation and/or apoptosis but does not play a role in maintaining the differentiated cell state. Moreover, NFI-C2 up-regulates *TP53* expression in the mammary gland during pregnancy [113]. Therefore, NFI-C2 likely functions as a protector against tumorigenesis during epithelial cell proliferation in mammary gland development.

3.4 Other carcinomas

Mis-regulation of the NFI transcription factors, or genomic aberrations that affect their gene loci, have also been observed in other carcinomas such as esophageal squamous cell carcinoma, hepatocellular carcinoma, and renal cell carcinoma (Table 3, Table 4). Based on current evidence, NFI transcription factors have both oncogenic and tumour suppressor potential, depending on the carcinoma type and its tissue of origin (Table 4). However, how the NFI transcription factors function in the development of these tissue types, and how this coincides with their role in carcinoma requires further investigation.

4. Hematopoietic Tumours

In the case of non-solid tumours, the NFI transcription factors have been implicated in hematopoietic tumours that include myeoloproliferative neoplasms, leukemia, and lymphoma. Specifically, point mutations, focal deletions, and translocations of *NFIA* have been found in myeloproliferative neoplasms [114, 115] and acute erythroid leukemia [116] (Table 3). Loss of *NFIB* due to 9p LOH was also reported in approximately 30% of myeloproliferative neoplasms [117-119], and in T-cell lymphomas (Sézary syndrome) [120]. These findings suggest a possible role for NFI in hematopoietic tumour development, as corroborated for T-cell lymphomas in an insertional mutagenesis mouse model where insertions within *Nfia*, *Nfib* and *Nfic* occur [121] (Table 2a).

During development, NFIA is an important regulator of hematopoiesis, particularly in lineage fate decisions. *NFIA* overexpression, coupled to induced differentiation, is associated with megakaryocyte-erythroid progenitor differentiation [26, 27], whereas its down-regulation is associated with granulocyte-monocyte progenitor differentiation [27-29]. Low NFIA expression in cells committed to the granulocyte-monocyte lineage further drives these cells to undergo monocytic differentiation [30, 31]. As a regulator of hematopoietic lineage commitment, disruption of NFIA could lead to the de-regulation of hematopoiesis. One possible outcome of this is uncontrolled erythroblastosis [116], ultimately contributing to the development of acute erythroid leukemia or myeloproliferative neoplasms [114, 115].

NFIB and NFIC are also required to drive megakaryocyte differentiation from megakaryocyte-erythroid progenitors. NFIB expression is up-regulated during induced

differentiation of megakaryocyte-erythroid progenitors [29], and megakaryocytes demonstrate increased expression of *NFIB* and *NFIC* [122, 123]. Loss of *NFIB* or *NFIC* in megakaryocyte progenitors is sufficient to prevent their differentiation, whereas their overexpression increases cell maturation [124]. Therefore, the excessive erythroblastosis in polycythemia vera could be attributed to defective megakaryocyte differentiation as a consequence of loss of NFIB [117-119].

On the other hand, NFIX expression promotes myeloid lineage progression and suppresses lymphoid development in hematopoietic progenitors [125]. Loss of *Nfix* also causes apoptosis in murine hematopoietic stem cells [126]. However, its importance in hematopoietic tumours is yet to be investigated. Taken together, the NFI transcription factors are essential in regulating lineage progression, differentiation, and the survival of hematopoietic cells. The dysregulation of these proteins may contribute to hematopoietic tumour growth.

5. Other Tumours

NFI transcription factors have also been implicated in other tumour types such as melanoma, osteosarcoma, neurofibroma, and benign tumours, although their role in these tumours is less clear. In human melanomas, genomic aberrations within the *NFI* genes, including single nucleotide polymorphism and translocations, have been observed [127-129] (Table 1, Table 3). Insertions within *Nfia* were also observed in tumours derived from an insertional mutagenesis melanoma mouse model [130] (Table 2a), suggesting that NFIA could act as a tumour suppressor in melanoma. NFIB expression, on the other

hand, correlates with more aggressive melanomas and promotes melanoma cell migration and invasiveness [35], suggesting that NFIB acts as an oncogene in this case. However, this role is contradicted by the inability of NFIB-overexpressing cells to form tumours when xenografted into immune-compromised mice [35]. Functional studies using uveal melanoma cells that originate from the same cell population that gives rise to cutaneous melanoma [131] have demonstrated that overexpression of NFIB and NFIC promotes cell migration and metastasis through suppression of an integrin subunit [132]. Inducing human melanoblast differentiation during development results in the down-regulation of NFIB expression [35], and its deletion in mice enhances melanocyte stem cell self renewal [36]. These findings demonstrate that NFIB expression is important in maintaining the quiescent state of melanocyte stem cells. This may explain why overexpression of NFIB in a pre-cultured melanoma cell line is insufficient to form xenograft tumours in mice [35].

In human osteosarcomas, a missense coding SNP in *NFIB* and decreased *NFIB* expression have been associated with increased metastasis [133] (Table 1). A direct role for loss of NFIB in metastatic disease is substantiated by increased cell migration *in vitro* when *NFIB* levels are decreased [133] and the identification of disrupting insertions in *Nfib* in metastases collected from an insertional mutagenesis osteosarcoma mouse model [134] (Table 2a). These findings suggest that disruption of NFIB contributes to the osteosarcoma metastasis. This function is similar to its role in osteoblast development. In human osteoblast and bone formation, NFIB and NFIC are highly expressed and transcriptionally regulate cell proliferation, differentiation and survival through insulin-like growth factor binding proteins [32]. In addition, the disruption of NFIC causes

defects in bone formation due to the failure of osteoblast differentiation and epithelial cell migration [33, 34]. Reduced expression of *NFIC* is also observed in dedifferentiated osteosarcoma cells [135]. These findings suggest that disruption of the NFI transcription factors perturbs cell differentiation and migration, possibly leading to tumorigenesis and metastasis.

The NFI transcription factors have also been implicated in benign tumours, although the reasons for this remains unclear. For example, disruption of NFI promotes the progression of benign neurofibromatosis to malignant peripheral nerve sheath tumours as shown in insertional mutagenesis mouse models where insertions within *Nfia* or *Nfib* were identified [136] (Table 2a). In other benign tumours, only translocations involving *NFIB* have been reported, such as the *HMGA2-NFIB* translocations that are commonly found in lipoma [137, 138], pleomorphic adenoma [139], and uterine leiomyoma [140, 141] (Table 3). Interestingly, the *MYB-NFIB* fusion that is characteristic of AdCC is also found in dermal cylindroma (Table 3), suggesting that similar pathways may be maladapted in these disorders [142].

6. Discussion

6.1 The context-dependent roles of NFI in cancer

Advances in high-throughput sequencing technologies have resulted in the identification of aberrations affecting NFI expression or function in various cancer types. Hence, there is now a body of evidence to suggest that the NFI family of transcription factors have both oncogenic and tumour-suppressive potential, depending on the context. This holds

true across different tumour types, but also applies to the role of the different NFI family members within a single tumour type. For instance, NFIB may be oncogenic in ER-negative breast cancers and SCLC, but likely functions as a tumour suppressor in AdCC and GBM. Similarly, although it has been reported that high expression of both *NFIA* and *NFIB* correlates with improved clinical outcome and lower grade astrocytomas [37, 38], other studies have suggested that NFIA and NFIB can function in opposing roles. *In vivo* overexpression of NFIA in glioma promotes cell proliferation and tumour growth [200, 201], whereas overexpression of NFIB induces differentiation, thereby halting tumour growth [38]. Finally, a single NFI transcription factor can perform opposing roles within the same tumour type, depending on the molecular context. Overexpression of NFIB inhibits cell proliferation and tumour growth by activating phospho-STAT3 signalling in STAT3-expressing GBM, but not in GBM without STAT3 expression [38]. It is likely that these differences are due to the transcriptional and post-translational regulation of the *NFI* genes themselves, and their subsequent recruitment of different molecular/protein co-activators or co-repressors to regulate downstream transcription. These differences accentuate the need to understand tumour context and the molecular pathways involved before assigning a function to specific NFI transcription factors in different cancer types. More importantly, careful consideration is required when targeting signalling pathways during treatment, as misapprehensions and poor treatment choice could in fact accelerate tumour progression.

6.2 Regulatory mechanisms governing NFI expression

NFI genes have been shown to be regulated in a variety of cancers through changes in gene copy number, both amplification of the gene and LOH, which alter mRNA expression, but this can also be altered via methylation and microRNA's. Amplification of the *NFIB* locus and corresponding high *NFIB* expression have been reported in SCLC [85, 86], ER-negative breast carcinoma [94-98], and esophageal squamous cell carcinoma [196], suggesting that NFIB functions as an oncogene in these tumour types. In contrast, LOH or deletions causing low *NFIB* expression is common in astrocytomas [42-46], myeloproliferative neoplasms [117-119], T-cell lymphomas [120], and hepatocellular carcinoma [166, 197]. Similarly, LOH and low *NFIA* expression was found in oligodendroglioma [52-54], myeloproliferative neoplasms [114, 115], and hepatocellular carcinoma [166, 197]. These studies suggest potential roles for *NFIA* and *NFIB* as tumour suppressors, which are also corroborated in insertional mutagenesis mouse models (Table 2a), as well as *in vitro* and *in vivo* studies [37, 38].

Promoter methylation of the different *NFI* promoters has not been well studied in the context of cancer. In a recent study of NSCLC samples with low *NFIB* expression, *NFIB* promoter hypermethylation was not observed, and only 6% of samples demonstrated *NFIB* copy number loss [90]. In these samples, *NFIB* was down-regulated as a result of tumour specific expression of miR-212 and miR-92b [90]. These findings suggest that microRNA dysregulation may be a common pathway resulting in *NFI* down-regulation in cancer.

The *NFI* loci are targeted by a number of miRNAs that are dysregulated in cancer, such as miR-21, miR-223, miR-124, miR-129, and miR-191 [28, 90, 153, 202-205]. For instance, expression of miR-124 and miR-129 in astrocytoma is inversely correlated with expression of their target *NFIB* and increased tumour grade [153, 205, 206]. Although *in vitro* experiments have demonstrated microRNA regulation of *NFI* in tumour cells in these cases [28, 90, 153, 202-204], the importance of *NFI* as a target *in vivo* remains to be determined.

6.3 Structural variations alter function of NFI proteins

The expression of naturally occurring NFI isoforms due to alternative mRNA splicing, particularly at the C-terminus transactivation domain (Fig. 1), might be a key determinant of the function of NFI proteins in development and cancer. Most differences between isoforms occur in the C-terminal transactivation and repression domain, and are likely to alter protein function. For example, the NFI-X1 isoform (Fig. 1, NFIX variant iv), in which exon 9 is skipped, is not able to induce glial fibrillary acidic protein (GFAP) expression [207]. On the other hand, the full length NFI-X3 isoform (Fig. 1, NFIX variant ii) can induce the expression of GFAP, resulting in astrocytic differentiation from neural progenitors [207]. This isoform also promotes the migration of glioma cells *in vitro* [11]. Some isoforms completely lack the DNA binding domain or transactivation domain and arelikely to result in the loss-of-function of these proteins. For example, the NFI-B3 isoform (Fig. 1, NFIB variant vii) lacks a transactivation domain and consists only of a truncated DNA binding domain. This isoform is able to bind to its motif in

DNA but does not activate gene transcription [7], suggesting that it may act as a dominant negative isoform and antagonise normal NFI function. Given that little is known about the precise function or expression of the different NFI isoforms, expression of specific NFI isoforms may explain the contradictory roles observed in some cancer types, such as thatof NFIB in SCLC and NSCLC. More in-depth analyses of available mRNA-sequencing data or proteomic analyses will be required to understand the function of NFI genes in different tumour contexts.

6.4 Potential role of post-translational modifications on NFI protein function

A further layer of complexity that requires consideration is how post-translational modifications of the NFI transactivation domain may affect their function (Fig. 1). For instance, phosphorylation of NFI is required to induce the expression of glial differentiation markers in glioma cells [15, 16], whereas glycosylation of NFI is mandatory in activating the transcription of whey acidic protein [8], and recruiting co-activators, repressors or other nuclear regulatory targets [14] during mammary gland development. In contrast to its role in mammary gland development, glycosylation appears disruptive for NFI function in the differentiation of skin keratinocytes [13], suggesting that glycosylation of NFI could confer multiple functions. A major limitation of these studies is that they have not identified the exact amino acid residues that are modified [8, 12-16]. Other post-translational modifications of NFI, including SUMOylation [12] and acetylation [208], are also observed. However, similar to NFI phosphorylation, the physiological functions of these modifications have not been

determined. Hence, proteomic analyses such as mass spectrometry will be useful for identifying the presence of NFIpost-translational modifications in order to obtain a more accurate interpretation of NFI function in cancer.

6.5 Potential impact of mutations on NFI function in cancer

Mutations provide another scenario through which NFI function is altered in cancer. The most prevelant *NFI* mutation is the translocation of *NFIB* and *MYB* or *MYBL* in AdCC (Table 3). The presence of other translocation partners and nonsense mutations affecting *NFIB* in AdCC [70, 75, 78-82] suggest that NFIB may act as atumour suppressor in this tumour type. Although many other translocations involving *NFI* have been reported (Table 3), their functional consequence or relevance remains to be determined.

Missense mutations in the*NFI* locihave been observed in up to 10% of melanoma and uterine carcinoma samples[209-211]. How these mutations affect NFI function remains to be determined, butno clear mutational hotspots or recurrent mutations are reported. It is likely that many of these mutations are passenger mutations due to the high mutation rate in some cancer types.

Truncating mutations of *NFI* genes are uncommon, but have been reported for tumours in which a tumour suppressor role has been proposed, including AdCC [70], medulloblastoma [212], and GBM [184]. Such mutations may function as dominant negative mutations if they result in an antagonising function similar to NFI-B3. Thus, these mutations may provide additional evidence for the proposed role of NFI in these specific tumour types.

6.6 The convergent roles of NFI in development and cancer

Despite these challenges, the role of the NFI transcription factors in regulating the balance between cellular proliferation and differentiation/quiesence during development appears conserved in the context of cancer. This is advantageous as it allows us to consider how the normal function of these genes might be disrupted in cancer, particularly in relation to tumour initiation and progression. For example, the NFI transcription factors and STAT3 bind to the GFAP promoter to drive astrocytic differentiation during development [213]. An appreciation of this relationship proved useful in our discovery that STAT3 is required for NFIB to inhibit proliferation in glioblastoma both *in vitro* and *in vivo* [38]. Similarly, the antagonistic relationship between SOX10 and NFIA in regulating glioma subtypes resembles their role in the lineage progression of glial cells during development [55].

In conclusion, the role of the NFI transcription factors in development is highly convergent with their role in cancer when their expression is disrupted. Also, there is appears to be a tendency for the NFI transcription factors to be implicated in tumours that arise from cells that normally express the concordant transcription factor during development. We posit that an in-depth understanding of the correlation between NFI function indevelopment and tumorigenesis will contribute greatly to understanding NFI function in cancer, and may ultimately be of prognostic and therapeutic value in overcoming these diseases.

Conflict of interest statement

The authors declare no conflicts of interest.

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Figure 1 Schematic representations of the structural variability of the NFI transcription factors. Each exon is represented relative to its totalamino acid length. All NFI family members share a highly conserved DNA-binding and dimerization domain at their N-termini (green box). The exon 1 region is variable due to alternative transcriptional start sites. The C-termini of the NFI proteins vary between family members and also between isoforms. Variants with similar structure, differing onlu in exon 1 are represented with a single variant. Boxes that have been lightly coloured represent exons with alternative reading frames within the same exonic region. Commonly detected phosphorylation and acetylation sites are portrayed in this figure [208]. Variants with corresponding ENSEMBL spliced transcript ID adopted from GENCODE v24 [214] are outlined in Supplementary Table 1.

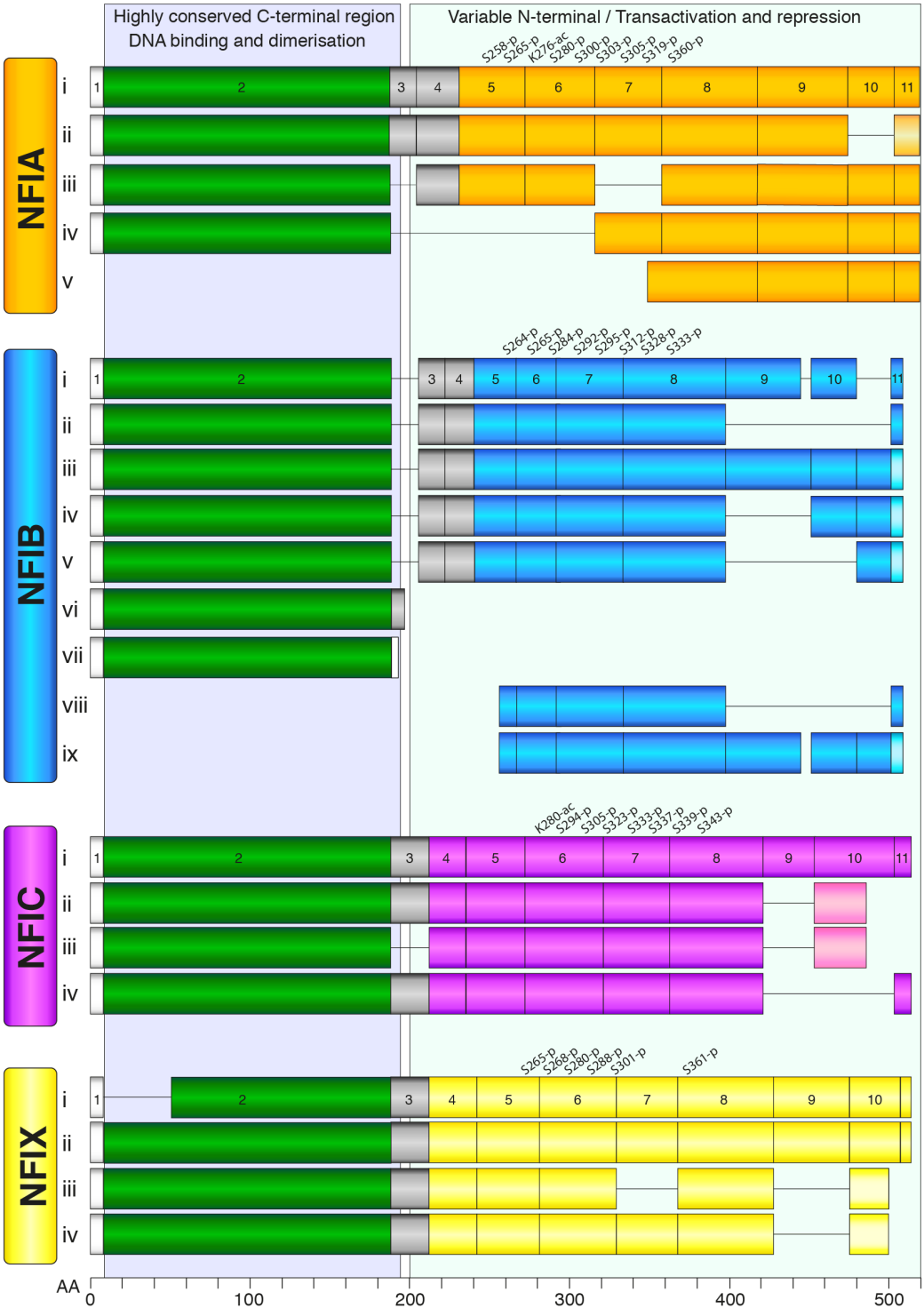
Highly conserved C-terminal region
DNA binding and dimerisation
Variable N-terminal / Transactivation and repression
NFIA
NFIB
NFIC
NFIX
i
ii
iii
iv
v
vi
vii
viii
ix
S258-p
S265-p
K276-ac
S280-p
S300-p
S303-p
S305-p
S319-p
S360-p
S264-p
S265-p
S284-p
S292-p
S295-p
S312-p
S328-p
S333-p
K280-ac
S294-p
S305-p
S323-p
S333-p
S337-p
S339-p
S343-p
S265-p
S268-p
S280-p
S288-p
S301-p
S361-p
AA
0
100
200
300
400
500

Figure 2 Organ systems in which the NFI genes are implicated, both during development and in cancer. During development, the NFI transcription factors are important for cell proliferation, differentiation, migration and lineage progression. These genes are also reported to function as oncogenes or tumour suppressor genes (TSG) in cancer, depending on the cellular and molecular contexts.

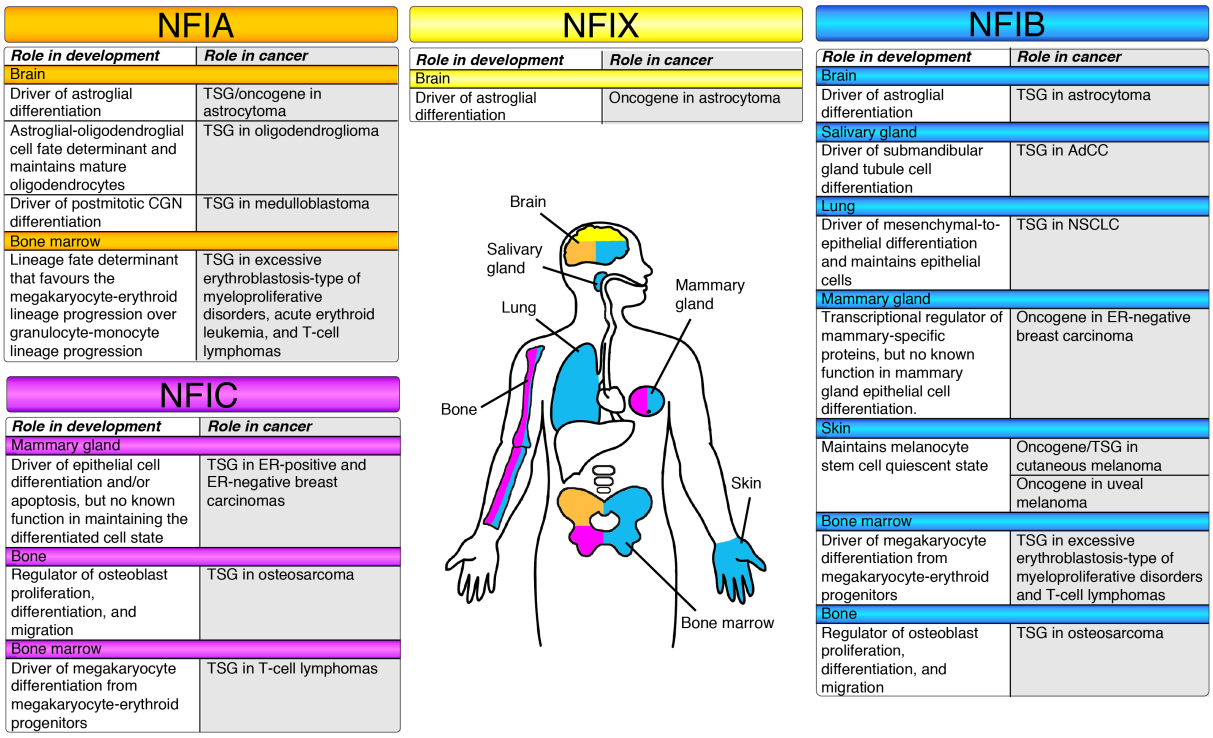

Table 1 Association of NFI expression with human tumour subtype, progression, cell characteristics, and response to treatment.

Tumour Type	NFI Member	Association	Findings	Reference
Bladder cancer	NFIA	Tumour progression	Elevated *NFIA* mRNA expression is associated with T1 progressive bladder cancer, compared with T1 nonprogressive tumours.	Sharron Lin et al., 2014 [143]
	NFIB	Response to treatment	High *NFIB* mRNA expression is associated with oxaliplatin resistance in bladder cancer.	Kashiwagi et al., 2011 [144]
Breast cancer	NFIB	Response to treatment	High *NFIB* mRNA expression in primary breast cancer tumour samples is associated with a good pathologic response to neoadjuvant chemotherapy.	Oh et al., 2014 [145]
Breast cancer (ER-negative)	NFIB	Response to treatment	High *NFIB* mRNA expression in ER-negative breast cancer tumour samples is associated with a good pathologic response to taxane-anthracycline chemotherapy.	Hatzis et al., 2011 [99]
		Subtype	High *NFIB* mRNA expression is associated with ER-negative subtype of breast cancer.	Moon et al., 2011 [95], Smith et al., 2008 [96]
Colorectal cancer	NFIB	Response to treatment	High *NFIB* mRNA expression is associated with oxaliplatin resistance in colorectal cancer.	Kashiwagi et al., 2011 [144]
	NFIX	Response to treatment	*NFIX* expression is associated with chemotherapy resistance in colorectal cancer patients.	Hu et al., 2016 [146]
Embryonal tumours with multilayered rosettes	All NFI members	Subtype	Low mRNA expression of NFI transcription factors is associated with *C19MC* amplified/LIN28+ embryonal tumours with multilayered rosettes.	Spence et al., 2014 [147]
Epithelial ovarian cancer	NFIB	Response to treatment	High *NFIB* mRNA expression is associated with a good pathologic response to chemotherapy.	Liu et al., 2012 [148], Spentzos et al., 2005 [149]

Giant cell tumour of bone	NFIB	Tumour progression	Elevated *NFIB* mRNA expression is associated with metastatic giant cell tumour of bone samples.	Mosakhani et al., 2013 [150], Quattrini et al., 2015 [151]
Glioma				
Astrocytoma	NFIA	Cell characteristics	*NFIA* is a transcriptional signature of a stemlike compartment in single-cell transcriptional profiles of primary glioblastoma tumours.	Patel et al., 2014 [152]
		Grade	Low *NFIA* mRNA expression is associated with increased tumour grade.	Song et al., 2010 [37]
		Survival	High *NFIA* mRNA expression is associated with better progression-free survival in patients with high-grade astrocytomas.	Song et al., 2010 [37]
	NFIB	Cell characteristics	NFIB is a transcriptional signature of a stemlike compartment in single-cell transcriptional profiles of primary glioblastoma tumours.	Patel et al., 2014 [152]
		Grade	Low *NFIB* mRNA expression is associated with increased tumour grade.	Stringer et al., 2016 [38]
		Survival	High *NFIB* mRNA expression is associated with better overall survival in patients with high-grade astrocytomas.	Stringer et al., 2016 [38]
		Subtype	Low *NFIB* mRNA expression is associated with mesenchymal subtype of glioblastoma.	Stringer et al., 2016 [38]
Astrocytoma (pediatric)	NFIB	Subtype	*NFIB* protein and mRNA expression is higher in anaplastic pilocytic astrocytoma (PA), compared with sporadic PA and NF1-PA. No strong *NFIB* expression is observed in dffuse glioma and non-neoplastic brain.	Ho et al., 2013 [153]
Oligodendroglioma	NFIA	Glioma subtype	The percentage of NFIA-expressing cells in oligodendrogliomas is consistently lower than in astrocytomas.	Song et al., 2010 [37]
			Low *NFIA* mRNA expression is associated with oligodendrogliomas.	Sun et al., 2014 [51]

Hepatocellular carcinoma	NFIB and NFIC	Subtype	High *NFIB* and *NFIC* mRNA expression is associated with hepatocellular carcinoma subclass S3.	Hoshida et al., 2009 [154]
Melanoma	NFIA	Tumour progression	Low *NFIA* expression is associated with metastatic melanoma, compared with primary tumours.	Kauffmann et al., 2008 [155]
	NFIB	Tumour progression	Lowered *NFIB* expression is associated with metastatic melanoma, compared with primary tumours.	Jaeger et al., 2007 [156]
Oropharyngeal squamous cell carcinoma	NFIA	Response to treatment	Disruption of NFIA is associated with irresponsiveness to therapy.	Walline et al., 2016 [157]
Osteosarcoma	NFIB	Tumour progression	Lowered *NFIB* expression due to single nucleotide polymorphism is associated with increased osteosarcoma metastasis.	Mirabello et al., 2015 [133]
Small cell lung cancer	NFIB	Subtype	High expression or amplification of *NFIB* was observed in both human and mouse primary small cell lung cancer tumours and cell lines.	Dooley et al., 2011 [85], Iwakawa et al., 2013 [86]
Uveal melanoma	NFIB	Tumour progression	Lowered *NFIB* mRNA expression is associated with aggressive class 2 uveal melanomas.	Onken et al., 2006 [158]

Table 2 The NFI transcription factors are implicated in multiple mouse models of cancer.

a. *Insertional mutagenesis mouse models identifying common insertion sites within the Nfi loci*							
Tumour type	Number of tumours analysed	Number of observed insertions				Frequency (%)	Reference
		Nfia	***Nfib***	***Nfic***	***Nfix***		
Breast cancer							
Triple negative	39	12	13		5	≥33%	Rangel et al., 2016 [159]
Breast cancer	33	1	13		1	45%	Suarez-Cabrera et al., 2017 [160]
Invasive lobular breast carcinoma	99				8[#]	8%	Kas et al., 2017 [161]
Colorectal cancer	446	50	65			22%	March et al., 2011 [162]
	17	≥1*	≥1			≥12%	Takeda et al., 2015 [163]
	31	≥1*	≥1			≥6%	Takeda et al., 2015 [163]
	37	≥1*	≥1			≥5%	Takeda et al., 2015 [163]
Glioma							
Glioblastoma	6	1	1			33%	Vyazunova et al., 2014 [39]
Non-glioblastoma	27	2				7%	Vyazunova et al., 2014 [39], Bender et

							al., 2010 [40]
Mixed	108	1	1	1	5	7%	Johansson et al., 2004 [41]
Hepatocellular carcinoma	228	174*	141		25	≥76%	Bard-Chapeau et al., 2014 [164]
	106	35	26			≥33%	Kodama et al., 2016 [165]
	48	17				35%	Kodama et al., 2016 [165]
Hepatocellular preneoplastic nodule	68	3	4*		2	18%	Keng et al., 2009 [166]
Leukemia	65	7	3			15%	Heltemes-Harris et al., 2016 [167]
Lymphoma	467	9				2%	Kool et al., 2010 [165], Uren et al., 2008 [166]
Malignant peripheral nerve sheath tumour	106	9	6			13%	Rahrmann et al., 2013 [136]
Medulloblastoma (SHH subtype)	85	22*			18	47%	Genovesi et al., 2013 [58]
	41	22*	7#			59%	Lastowska et al., 2013 [59]
	139	51	27		8	≥37%	Wu et al.,

							2012 [60]
Melanoma	278	9				35	Perna et al., 2015 [130]
	43		1			2%	de la Rosa et al., 2017 [168]
	82		1			1%	de la Rosa et al., 2017 [168]
Neurofibroma	269	55	40			31%	Rahrmann et al., 2013 [136]
Osteosarcoma	119		17*			11%	Mirabello et al., 2015 [133]
	23		1			4%	Moriarity et al., 2015 [134]
	14		1		1	14%	Temiz et al., 2016 [169]
Pancreatic ductal adenocarcinoma	198	26	44			≥22%	Perez-Mancera et al., 2012 [170]
	42		7			17%	Mann et al., 2012 [171]
Prostate cancer	45		1			2%	de la Rosa et al., 2017 [168]
	82	1	1			2%	de la Rosa et al., 2017 [168]
Thymic lymphoma	101	3	2	1		6%	Berquam-Vrieze et al., 2011

							[121]
b. *Transgenic mouse models with observed copy number alterations in Nfi*							
Tumour type	Number of tumours analysed	Number of observed copy number gain				Frequency (%)	Reference
		Nfia	***Nfib***	***Nfic***	***Nfix***		
Prostate cancer	5		4[#]			80%	Zhou et al., 2006 [172]
Small cell lung carcinoma	17		4[#]			24%	Dooley et al., 2011 [85]
c. *Correlation of NFI expression level with tumour latency, metastasis, and median survival in transgenic mouse models with altered NFI expression*							
Tumour type	NFI member	Alteration of expression level	Findings				Reference
Medulloblastoma	*Nfia**	Reduced expression	Mice with reduced expression of *Nfia* demonstrated a significant decrease in tumour latency.				Genovesi et al., 2013 [58]
Small cell lung carcinoma	*Nfib*[#]	Overexpression	Mice with overexpression of *Nfib* demonstrated a significant decrease in tumour latency and more extensive metastasis.				Semenova et al., 2016 [88]
	Nfib[#]	Overexpression	Mice with overexpression of *Nfib* demonstrated a significant decrease in median survival.				Wu et al., 2016 [89]

> Based on publication precise number is unknown, but minimal number represented

[#] Predicted as oncogene by the authors.

* Predicted as tumor suppressor gene by the authors.

Table 3 Translocations of NFI in various tumours and cancer cell lines.

Tumour Type	NFI	Fusion	Tumour Location	Cases	Reference
Adenocarcinoma	NFIA	DCLK1	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		FAF1	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		FGGY	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		HYI	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		LTV1	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		ST6GALNAC3	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		EHF	Breast cancer*	1	Asmann et al., 2011 [173], Ha et al., 2011 [174], Klijn et al., 2015 [175], Robinson et al., 2011 [176], Stephens et al., 2009 [177]
		ATG4C	Ovarian serous cystadenocarcinoma	1/400	Yoshihara et al., 2015 [75]
		INADL	Ovarian serous cystadenocarcinoma	1/400	Yoshihara et al., 2015 [75]
		CYP2J2	Prostate adenocarcinoma	1/178	Yoshihara et al., 2015 [75]
		ZNF253	Rectum adenocarcinoma	1	Yoshihara

					et al., 2015 [75]
	NFIB	HEATR5B	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		MYB[#]	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		MPDZ	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		STRN	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		ZDHHC21	Lung adenocarcinoma	1/487	Yoshihara et al., 2015 [75]
	NFIC	FZR1[#]	Breast cancer	2/1019	Yoshihara et al., 2015 [75]
		LRTOMT	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		WDR18	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		CELF5[#]	Ovarian cancer*	1	Yoshihara et al., 2015 [75]
	NFIX	DAND5	Breast cancer	2/1019	Yoshihara et al., 2015 [75]
			Lung adenocarcinoma	1/487	Yoshihara et al., 2015 [75]
		MAST1[#]	Breast cancer	1/13	Robinson et al., 2011 [176]
		MCU	Breast cancer	1/1019	Yoshihara et al., 2015 [75]
		TBCD	Breast cancer	1/1019	Yoshihara et al., 2015 [75]

		BSG	Breast cancer*	1	Edgren et al., 2011 [178]
		GCDH	Breast cancer*	1	Klijn et al., 2015 [175]
			Lung adenocarcinoma	1/487	Yoshihara et al., 2015 [75]
		ANKRD40	Endocervival Adenocarcinoma	1	Yoshihara et al., 2015 [75]
Adenoid cystic carcinoma	NFIB	MYB[#]	Breast	4/4	Persson et al., 2009 [73]
			Breast	10/12	Martelotto et al., 2015 [179]
			Breast	2/4	Brill et al., 2011 [68]
			Breast	6/31	D'Alfonso et al., 2014 [180]
			Breast	12/13	Wetterskog et al., 2012[181]
			Head and neck	7/7	Persson et al., 2009 [73]
			Larynx	2/5	Brill et al., 2011 [68]
			Salivary gland	21/30	Brill et al., 2011 [68]
			Salivary gland	18/37	West et al., 2011 [74]
			Salivary gland	59/91	Rettig et al., 2015 [182]
			Salivary gland	32/60	Ho et al., 2013 [70]
			Salivary gland	39/102	Mitani et al., 2016 [80]
			Salivary gland	12/25	Rettig et al., 2016 [79]
			Salivary gland	8/20	Brayer et al., 2016

					[67]
			Salivary gland	16/33	Fujii et al., 2017 [76]
			Sinonasal cavity	5/7	Brill et al., 2011 [68]
			Trachea/bronchus	7/12	Brill et al., 2011 [68]
			Vulva	2/3	Brill et al., 2011 [68]
			Mix samples	3/8	Costa et al., 2014 [69]
		MYBL1	Salivary gland	12/102	Mitani et al., 2016 [80]
			Salivary gland	2/25	Rettig et al., 2016 [79]
			Salivary gland	3/20	Brayer et al., 2016 [67]
			Salivary gland	2/33	Fujii et al., 2017 [76]
		AIG1	Salivary gland	1/102	Mitani et al., 2016 [80]
		MAN1A1	Salivary gland	1/60	Ho et al., 2013 [70]
		MAP3K5	Salivary gland	2/25	Rettig et al., 2016 [79]
		MYO6	Salivary gland	1/25	Rettig et al., 2016 [79]
		NKAIN2	Salivary gland	1/102	Mitani et al., 2016 [80]
		PTPRD	Salivary gland	1/102	Mitani et al., 2016 [80]
		RIMS1	Salivary gland	1/25	Rettig et al., 2016 [79]
		RPS6KA2	Salivary gland	1/25	Rettig et al., 2016 [79]
		XRCC4	Salivary gland	1/102	Mitani et al., 2016 [80]
Other carcinomas	NFIA	SCP2	Non-small cell lung cancer*	1	Klijn et al., 2015 [175]
	NFIB	FREM1	Lung squamous cell carcinoma	1/220	Yoshihara et al., 2015 [75]
	NFIC	C16orf55	Adrenocortical carcinoma	1	Yoshihara

					et al., 2015 [75]
		FZR1[#]	Cervical squamous cell carcinoma	1	Yoshihara et al., 2015 [75]
		LSM7	Cervical squamous cell carcinoma	1	Yoshihara et al., 2015 [75]
		PIP5K1C	Hepatocellular carcinoma*	1	Klijn et al., 2015 [175]
		ZNF653	Lung squamous cell carcinoma	1/220	Yoshihara et al., 2015 [75]
	NFIX	DOCK6	Esophageal carcinoma	1	Yoshihara et al., 2015 [75]
		MAST1[#]	Lung carcinoma*	1	Klijn et al., 2015 [175]
		RALGPS1	Oral cavity squamous cell carcinoma	1	Yoshihara et al., 2015 [75]
			Head and neck squamous cell carcinoma	1/300	Yoshihara et al., 2015 [75]
		GATAD2A	Thyroid carcinoma	1/494	Yoshihara et al., 2015 [75]
Other cancers	NFIA	CBFA2T3	Acute erythroid leukemia	1	Micci et al., 2013 [116]
		NCOR1	Acute lymphoblastic leukemia	1/255	Liu et al., 2017 [183]
		RNLS	Glioblastoma	1/101	Frattini et al., 2013 [184]
				1/175	Shah et al., 2013 [185]
		AKD1	Medulloblastoma	1/79	Robinson et al., 2012 [186]
		TNNI3K	Melanoma	1/25	Berger et al., 2012 [127]
		RAF1	Pilocytic astrocytoma	1	Yde et al., 2016 [187]

	NFIB	C12orf42	Multiple myeloma	1/38	Chapman et al., 2011 [188]
	NFIC	CELF5[#]	Low-grade glioma	1/266	Yoshihara et al., 2015 [75]
		BRAF	Melanoma	1/531	Kim et al., 2017 [129]
	NFIX	MAST1[#]	Melanoma	1/25	Berger et al., 2012 [127]
		TNPO2	Melanoma	1/224	Cancer Genome Atlas, 2015 [189]
Benign tumours	NFIB	HMGA2	Lipoma	1	Pierron et al., 2009 [190]
			Lipoma	1/2	Nilsson et al., 2005 [138]
			Lipoma	2/29	Dadone et al., 2015 [191]
			Lipoma	2/5	Italiano et al., 2008 [137]
			Lipoma	1	Lacaria et al., 2017 [192]
			Pleomorphic adenoma	2/28	Asp et al., 2006 [193]
				2/2	Geurts et al., 1998 [139]
		MYB[#]	Dermal cylindroma	8/12	Fehr et al., 2011 [142]

Table 4 The putative roles of NFI in other carcinomas.

Carcinoma Type	NFI Member	Proposed Function	Findings	Reference
Cutaneous squamous cell carcinoma	NFIB	Tumour suppressor	Down-regulation of NFIB is common in both cell lines and tumour samples, and drives tumour progression.	Zhou et al., 2015 [194], Zhou et al., 2014 [195]
Esophageal squamous cell carcinoma	NFIB	Oncogene	NFIB locus is amplified in primary tumours and cell lines.	Yang et al., 2001 [196]
Hepatocellular carcinoma	NFIA	Tumour suppressor	Copy number loss of NFIA has been reported in tumours.	Keng et al., 2009 [166], Fujimoto et al., 2012 [197]
	NFIB	Tumour suppressor	Copy number loss of NFIB has been reported in tumours.	Keng et al., 2009 [166], Fujimoto et al., 2012 [197]
		Oncogene	Knockdown of NFIB inhibits tumour cell growth and promotes apoptosis.	Zhang et al., 2015 [198]
Renal cell carcinoma	NFIC	Oncogene	Up-regulation of NFIC is observed in tumour cell lines.	Takaoka et al., 2011 [199]

Supplementary Table 1 NFI variants and corresponding ENSEMBL spliced transcript IDs

NFI Transcription Factors	Variants	ENSEMBL Spliced Transcript ID
NFIA	i	ENST00000403491.7, ENST00000371191.5, ENST00000407417.7, ENST00000371189.8, ENST00000485903.6
	ii	ENST00000371187.7
	iii	ENST00000371185.6
	iv	ENST00000371184.6
	v	ENST00000357977.5
NFIB	i	ENST00000380953.5
	ii	ENST00000380959.7, ENST00000380934.8
	iii	ENST00000397575.7
	iv	ENST00000397581.6
	v	ENST00000397579.6
	vi	ENST00000380921.3
	vii	ENST00000622520.1
	viii	ENST00000380924.1
	ix	ENST00000543693.5
NFIC	i	ENST00000589123.5, ENST00000443272.2
	ii	ENST00000395111.7, ENST00000590282.5
	iii	ENST00000586919.5
	iv	ENST00000341919.7

NFIX	i	ENST00000588228.5
	ii	ENST00000592199.5, ENST00000585575.5
	iii	ENST00000358552.7, ENST00000360105.8
	iv	ENST00000397661.6, ENST00000587760.5, ENST00000587260.1