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Neurofibromatosis type 1 associated low grade gliomas: A comparison with sporadic low grade gliomas

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ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder, associated with a variable clinical phenotype including café-au-lait spots, intertriginous freckling, Lisch nodules, neurofibromas, optic pathway gliomas and distinctive bony lesions. NF1 is caused by a mutation in the NF1 gene, which codes for neurofibromin, a large protein involved in the MAPK- and the mTOR-pathway through RAS-RAF signalling.

Abbreviations: NF1, neurofibromatosis type 1; LGG, low grade glioma; MAPK, mitogen activated protein kinase; mTOR, mammalian target of rapamycin; PA, pilocytic astrocytoma; MPNST, malignant peripheral nerve sheath tumours; GAP, GTPase-activating protein; RB, retinoblastoma; GFAP, glial fibrillary acid protein; OPG, optic pathway glioma; JNK, c-Jun-Nh_2-kinase; FTI, Farnestyltransferase inhibitors.

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NF1 is a known tumour predisposition syndrome, associated with different tumours of the nervous system including low grade gliomas (LGGs) in the paediatric population. The focus of this review is on grade I pilocytic astrocytomas (PAs), the most commonly observed histologic subtype of low grade gliomas in NF1. Clinically, these PAs have a better prognosis and show different localisation patterns than their sporadic counterparts, which are most commonly associated with a KIAA1549:BRAF fusion.
In this review, possible mechanisms of tumourigenesis in LGGs with and without NF1 will be discussed, including the contribution of different signalling pathways and tumour microenvironment. Furthermore we will discuss how increased understanding of tumourigenesis may lead to new potential targets for treatment.

1. Introduction: neurofibromatosis type 1

Neurofibromatosis type 1 (NF1) or von Recklinghausen's disease is an autosomal dominant disorder with a worldwide incidence of 1 per 2500–3000 individuals. It is characterized by the presence of café-au-lait spots, intertriginous freckling, Lisch nodules, neurofibromas, optic pathway gliomas and distinctive bony lesions. Other features include malignant peripheral nerve sheath tumours (MPNSTs), neurocognitive defects, epilepsy and cardiovascular abnormalities (Williams et al., 2009). NF1 is caused by a mutation in the NF1 gene, located on chromosome 17q11.2 (Wallace et al., 1990; Viskochil et al., 1990). NF1 is a familial disorder with a mendelian inheritance pattern, but approximately half of the NF1 cases are caused by newly appearing mutations (Messiaen et al., 2000).

Although NF1 is an autosomal dominant disorder with 100% penetrance, there is a great variance in clinical presentation with relatively minor contribution of the nature of the NF1 mutation to disease expression. The only genotype-phenotype correlation that has been well established is that patients with an NF1 microdeletion have a more severe phenotype with higher incidence of neurofibromas and MPSNTs, a lower mean IQ, and distinct facial features (De Raedt et al., 2003; Wu et al., 1997). Other explanations for the great inter- and intrafamilial variation in NF1 may be environmental factors or the impact of modifier genes, such as mismatch repair genes. Cell lines with mutations in these genes show an increased number of somatic mutations of the NF1 gene, which may possibly lead to increased symptom load in patients carrying these mutations (Pasmant et al., 2012; Wang et al., 2003).

The NF1 gene codes for neurofibromin, a cytoplasmatic, 2818 amino acids containing protein. Neurofibromin is widely expressed throughout different tissues including neurons and astrocytes of the central nervous system, where it is believed to be involved in cortical development and astrocyte growth (Gutmann, 2002; Gutmann et al., 1991; Andersen et al., 1993; Zhu et al., 2001).

Neurofibromin is critically involved in different cellular processes through influencing signalling pathways. Firstly, neurofibromin promotes the conversion of ATP to cyclic AMP, where an absence of NF1 gene activity decreases c-AMP levels (Tong et al., 2002). Through this pathway, neurofibromin has a positive relationship with learning, life span and stress resistance in Drosophilia models (Tong et al., 2007; Guo et al., 2000) (Fig. 1).

Furthermore, neurofibromin acts as a negative regulator of RAS by functioning as a GTPase-activating protein (GAP), increasing the conversion of GTP-bound RAS to its GDP-bound form (Andersen et al., 1993; Basu et al., 1992). Loss of neurofibromin increases RAS activity and induces downstream activity of the MEK-ERK (MAPK, mitogen activated protein kinase) pathway as well as the PI3K-Akt-mTOR (mammalian target of rapamycin) pathway (Sandsmark et al., 2007; Banerjee et al., 2011a; Johannessen et al., 2005). Through these signalling pathways, neurofibromin functions as a negative regulator of cell growth and proliferation (Fig. 1).

2. NF1 and malignancies

NF1 is associated with an increased risk of malignancies, both nervous-system and non-nervous system related. Non-nervous system tumours include gastro-intestinal stromal tumours, duodenal carcinoids and phaechromocytomas as well as breast cancer and rhabdomyosarcomas. Nervous-system malignancies are both located in the central and peripheral nervous system. Malignant tumours of the peripheral nervous system include MPNSTs, most commonly arising from plexiform neurofibromas, and more rarely neuroblastomas (Brems et al., 2009). The lifetime risk of developing MPNSTs is 8–13% for NF1 patients and these tumours usually occur in adulthood (Evans et al., 2002).

The most common central-nervous system tumours in NF1 are low grade gliomas, with the optic pathway glioma being a hallmark lesion (Szudek et al., 2000). Higher grade gliomas are also more frequently found in NF1, but are almost only observed during adult life, while low grade gliomas are far more common in the paediatric population (Gutmann et al., 2002).

In most NF1-related malignancies, including astrocytomas, MPNSTs and neuroblastomas, biallelic inactivation of NF1 gene function is found in the affected cells (Upadhyaya et al., 2008; Origone et al., 2003; Gutmann et al., 2000). Somatic inactivation of the still functioning NF1 allele is believed to be required for tumour formation. This 'second hit' creates an absence of neurofibromin in affected cells, diminishing its normal functions, including those of controlling cell growth and proliferation. With this role of the NF1 gene as a tumour suppressor, it is not surprising that somatic mutations of the NF1 gene are also commonly found in different non NF1-associated tumours (Li et al., 1992).

In aggressive NF1-related tumours, such as MPNSTs and high grade gliomas additional mutations are found, such as mutations in TP53 and CDKN2A (Nielsen et al., 1999; Legius et al., 1994). These mutations may be important for the malignant transformation of relatively benign neurofibromas and astrocytomas, as is supported by mouse models where mice mutant for NF1 and Tp53 develop high grade gliomas (Reilly et al., 2004; Zhu et al., 2005a). CDKN2A (p16) and p53 are important in regulating cell cycle control by inhibiting cell cycle progression. Their activation is partially regulated by Ras through the Ink4/ARF locus, which encodes $p16^{INK4A}$ and $p19^{ARF}$. $p16^{INK4A}$ regulates the retinoblastoma (RB) protein, while $p19^{ARF}$ activates p53 by diminshed inhibition of Mdm2 (Fig. 1) (Lin and Lowe, 2001).

3. NF1 and low grade gliomas

3.1. Phenotype

Low grade gliomas are the most commonly found tumours of the central nervous system in the paediatric population, both in children with and without NF1. While these low grade gliomas have an excellent prognosis after gross total resection, they can