

NF1 Gene Mutation Mediates Neuronal Signaling De-Regulation Triggering Pediatric Optic Glioma Development: Another Small Step towards a Cure of NF1 Disorder?

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Pediatric optic pathway gliomas (OPGs) account for 20% of brain tumors [1].

These tumors are characterized by a low-grade growth and in some cases can be associated with a tumor predisposition syndrome. In particular, 15% of patients with neurofibromatosis type 1 (NF1) develop OPGs [2].

Sporadic and NF1-associated OPGs show different outcomes and are characterized by different radiological features [3], nevertheless both forms show activation of the MAPK (mitogen-activated protein kinase) and mTOR pathways.

The most common genetic lesion detected in sporadic OPGs is a genomic rearrangement leading to a formation of the chimeric BRAF-KIAA1549, in which is lost the BRAF regulatory amino terminal domain, while the kinase domain is maintained increasing activation of BRAF and the downstream MEK signaling cascade [4].

NF1-associated OPGs present a somatic bi-allelic inactivation of the NF1 tumor suppressor gene that is constitutionally inactivated in one of the two copies of NF1 patients [5].

Furthermore, a group of patients with OPGs showing typical radiological features of NF1-associated OPGs (NF1-like OPGs), but without the NF1 diagnostic criteria, have been identified. The genetic alterations rarely involve NF1 gene, differently from the expected, further mechanisms should be investigated to identify the conditions leading to NF1-like OPGs [6].

Recently, Pan and colleagues [7] carried out a mechanistic study, addressing the role of NF1 mutations in OPG onset, as well as the impact of environmental factors.

Neurons have been recently demonstrated to be important cellular constituents of the tumor microenvironment. Consistently, their activity enhances the growth and progression of different solid tumors [8]. Nevertheless, the role of neuronal activity in tumor initiation and the implication of NF1 gene mutation was little understood.

Pan and colleagues [7] used a mouse model of low-grade NF1-associated OPG with high tumour penetrance (> 95%) with a timeline of tumor progression similar to that of children with NF1-OPG [6]. The *Nf1^{flox/mut};Gfap::cre* genetically engineered mouse model recapitulates both the heterozygous germline NF1 mutation in stromal cells and the second hit somatic NF1 mutation in neural progenitor cells [9].

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They activated neuronal activity by optogenetically stimulating the optic nerve, to verify whether it has a role in the initiation of Nf1-OPGs. They observed that optic nerve activity is able to increase Nf1-OPG growth.

Light exposure during a specific developmental window of mice (6-16 weeks) promotes tumor growth.

Retinal activity increased secretion level of BDNF and NLGN3 and both factors increased the proliferation of low-grade glioma cells.

Why Nf1 heterozygous mutation is necessary for Nf1-OPG onset? Because Nf1 mutation aberrantly increases neuronal activity-regulated NLGN3 shedding in the optic nerve.

When NLGN3 shedding was blocked with GI254023X by ADAM10 inhibition in Nf1OPG mice or when Nf1OPG mice were dark reared from 6 to 16 weeks of age tumor formation and/or growth decreases.

The results obtained in Nf1OPG mice suggest a translational impact on OPG treatment in children with NF1 being ADAM10–NLGN3 axis a potential therapeutic target [9].

The provided findings will address pharmacological studies that should improve treatment of a specific phenotype of neurofibromatosis type 1, a disorder at now without an effective treatment.

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