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### How Loss of Neurofibromin in Oligodendrocytes Affects the Brain

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# How Loss of Neurofibromin in Oligodendrocytes Affects the Brain

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Neurofibromatosis type 1 patients are predisposed to central nervous system (CNS) phenotypes including enlarged brains, delayed acquisition of motor skills, brain tumors, and cognitive deficits. Imaging and pathologic analysis suggest that changes in white matter myelination may underlie both the enlargement of white matter tracts that contributes to megacephaly, and/or hyper-intense signals visualized on MRI. To study the role(s) of *Nf1* and HRas in oligodendrocytes, we examined the optic nerve and corpus callosum, myelinated fiber tracts. We studied *Nf1* heterozygous mice, tamoxifen-induced *Nf1* loss in mature oligodendrocytes (Plp-CreERT), and a new transgenic model in which the CNPase promoter drives expression of *HRasG12V*. Activated HRas and loss of *Nf1* within oligo-lineage cells (*PLPCre; Nf1fl+;* & *PLPCre; Nf1fl/fl*) resulted in optic nerve enlargement. The corpus callosum of *CNP-HRasG12V* mice was also enlarged. Electron microscopy analysis revealed 3 phenotypes within the enlarged optic nerves. 1) When *Nf1* was lost or HRas was activated within oligodendrocytes, the myelin was decompacted due to splitting at the intraperiod lines. The transgenic *Nf1+/-* mice, in which *Nf1* loss is not restricted to oligo-lineage cells, displayed lesser myelin decompaction, and these mice did not have significantly enlarged optic nerves. 2) Enlarged axons accompanied the decompacted myelin within all models. 3) All *Nf1* and Ras mouse models also showed an expansion of the perivascular astrocytic endfeet surrounding the vasculature. These phenotypes were also found within the corpus callosum. Thus, myelin and vascular phenotypes are not limited to a single myelinated fiber tract. These studies reveal a cell autonomous role for the *Nf1*/Ras pathway in the regulation of myelin compaction, and a non-cell autonomous role in the regulation of astrocytic endfeet surrounding brain capillaries.

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