C21orf91 as a new regulator of gliogenesis and Down syndrome neuropathology

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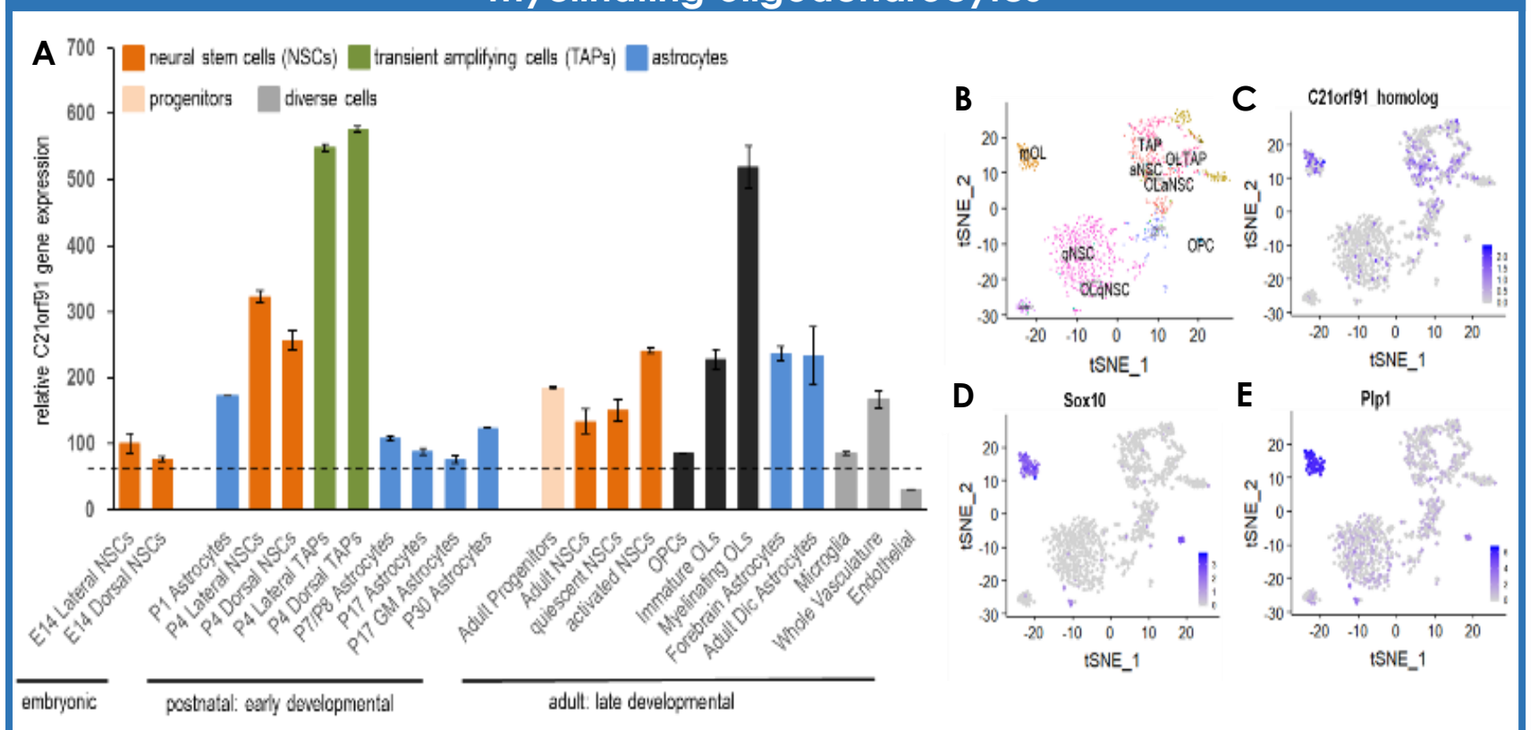
The neurological profile of Down syndrome (DS) – including intellectual disability (ID) – is characterised by hypotrophy and hypocellularity regarding neurons and oligodendrocytes, accompanied by hypomyelination and an over-population of astroglial cells (reviewed by Reiche L, et. al, 2019).
Genetic association studies revealed a dysregulated gene cluster in DS, including C21orf91 which is important for oligodendrogenesis (Olmos-Serrano JL, et al., 2016).
The present study aims to elucidate the role of C21orf91 in primary rat oligodendrocyte precursor cell (OPC) differentiation and analyse whether its modulation with special focus on the overexpression (as observed in DS patients) results in dysregulated oligodendrogenesis.

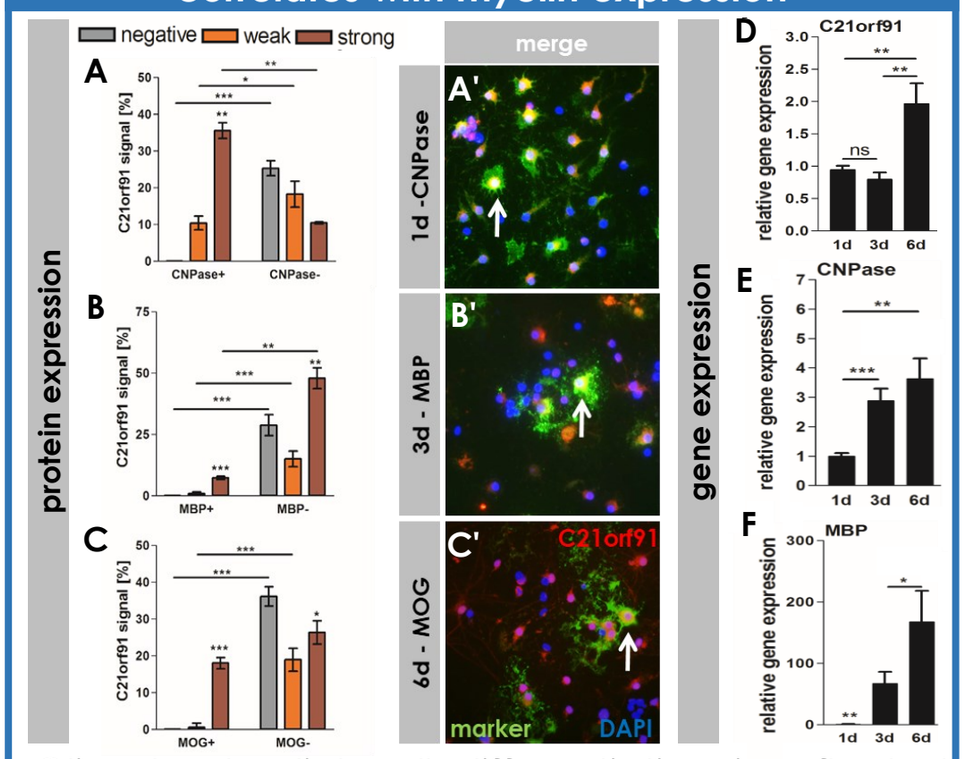
Physiological expression profile

Bioinformatics suggest that C21orf91 is essential for the generation of mature, myelinating oligodendrocytes



C21orf91 is highly expressed by transit amplifying progenitors (TAPs) and oligodendroglial lineage cells.

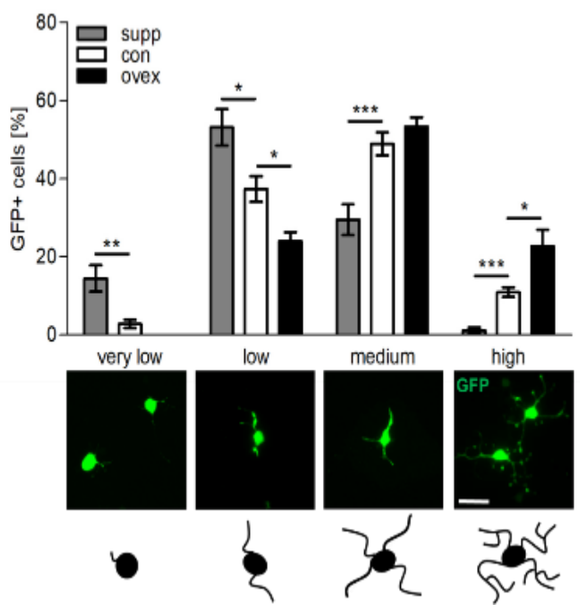
C21orf91 expression correlates with myelin expression



Oligodendroglial cell differentiation is reflected by the induction of myelin markers and C21orf91.

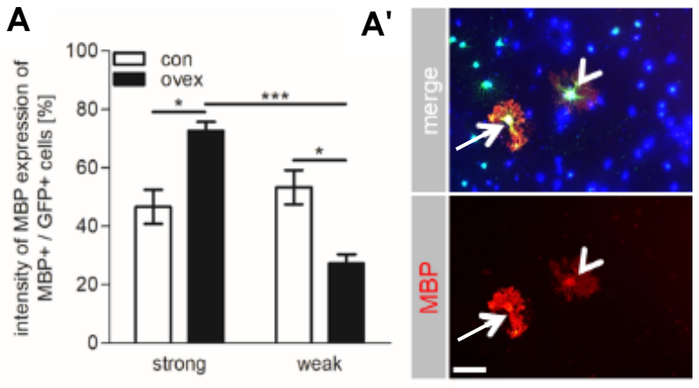
C21orf91 modulation upon C21orf91 modulation

C21orf91 modulation influences morphological maturation of OPCs



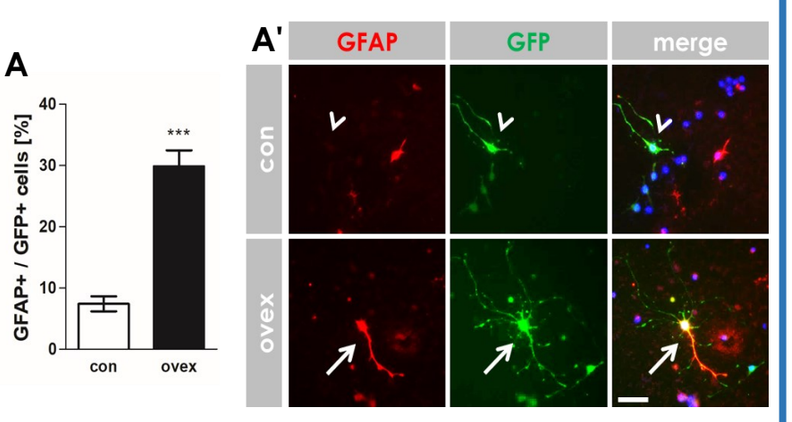
C21orf91 modulated OPCs cultured for two days in differentiation medium are categorised into different morphological stages. Transfection is visualised by GFP expression.

Overexpression results in higher MBP expression…



Immunostaining for MBP after three days in differentiation medium show a strong MBP expression in C21orf91 overexpressing cells compared to control transfected cells.

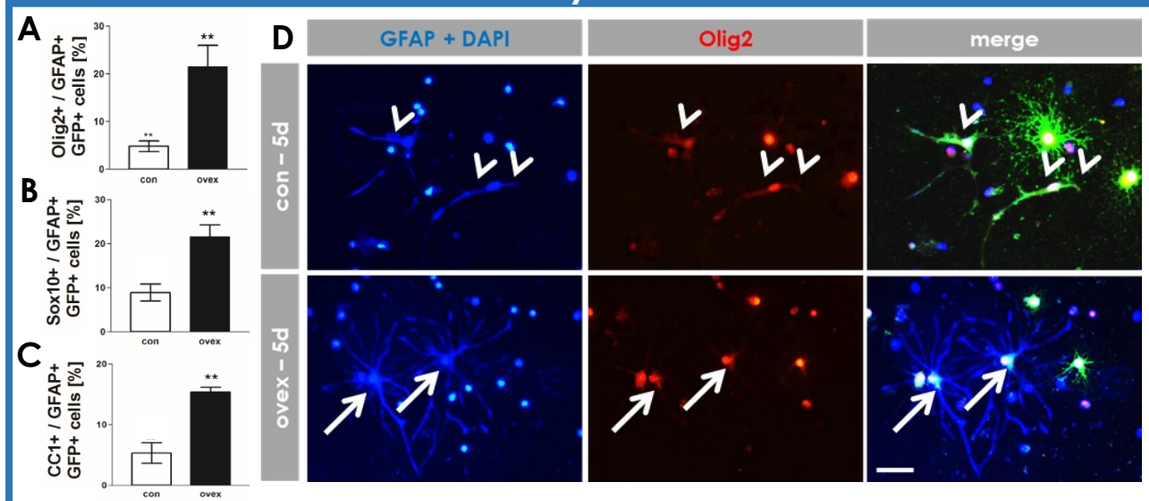
…but also increases GFAP expression...



Immunostaining for GFAP in C21orf91 overexpressing and control transfected cells after two days differentiation medium.

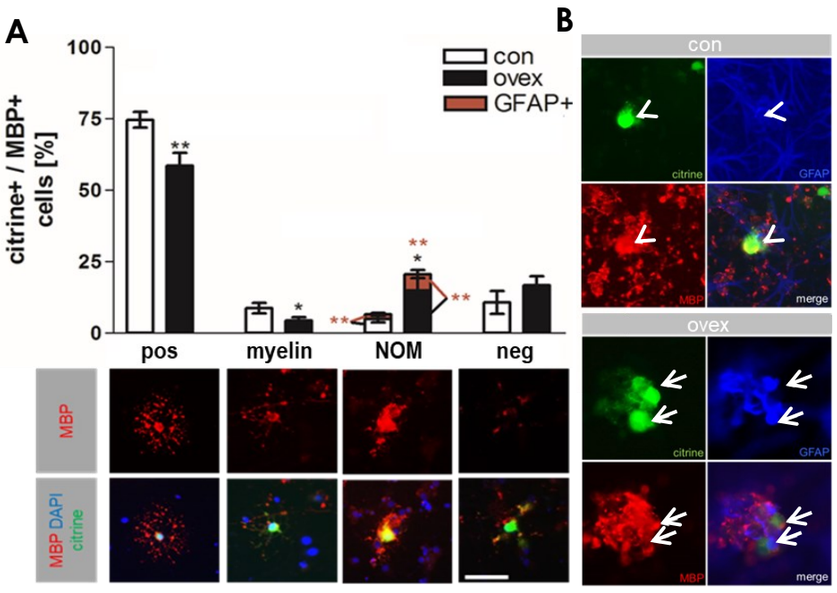
Differentiation

…increasing the number of atypical oligodendroglial cells with astrocytic features



Analysis for oligodendroglial lineage markers and GFAP upon C21orf91 overexpression during OPC differentiation. Hybrids even occur at late timepoints (5d, 10d).

C21orf91 overexpressing oligodendrocytes show myelination failures and coexpression of GFAP



Analysis of co-transfected OPCs 10 days after application on 15 days old CNS cocultures. Cells are categorised into different MBP-structure related differentiation stages. Non-organized MBP-expressing cells (NOM) show abnormal MBP and GFAP co-expression.

Conclusion

- Strong C21orf91 expression is correlated with oligodendroglial maturation and differentiation in culture.
- The modulation of C21orf91 results in either diminished or accelerated morphological maturation of OPCs.
- C21orf91 overexpressing oligodendrocytes exhibit atypical co-expression of lineage specific markers and the astrocytic marker GFAP.
- Although C21orf91 overexpressing oligodendrocytes show an increased MBP production, these cells have a diminished myelination capacity with a non-organised MBP-expression phenotype showing astrocytic features.

→ The regulation of C21orf91 expression is important for correct oligodendrocyte differentiation.

Disclosure

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