Persistent hypomyelination is not only a key symptom of patients with an inactive MCT8 but also represents a prominent feature in mice with a combined inactivation of the thyroid hormone (TH) transporters Mct8 and Oatp1c1 (so-called DKO mice). This phenotype might be explained by an impaired TH passage across the brain barrier cells and consequently, a profound TH deficiency in the CNS of these animals. Alternatively, combined Mct8/Oatp1c1 deletion may result in an impeded TH transport into oligodendrocytes and/or their precursor cells thereby compromising oligodendrocyte maturation and myelination.

To clarify the cell-specific function of Mct8/Oatp1c1 in myelin formation, we studied proliferation and differentiation pattern of oligodendroglia cells in mice lacking both TH transporters within the oligodendrocyte lineage only (so-called OL CKO mice) at different postnatal time points and included DKO animals for comparison. Immunofluorescence studies revealed normal expression of different mature myelin markers in adult OL CKO mice. However, at postnatal day 12, expression of these proteins was strongly reduced in OL CKO mice comparable to DKO animals suggesting a transient delay in myelination in these cell-specific TH transporter animals. We further enumerated Olig2/Pdgfra immunopositive oligodendrocyte precursor cells (OPC) as well as Olig2/CC1 expressing mature oligodendrocytes and could indeed detect a similarly reduced number of myelinating oligodendrocytes in OL CKO and DKO mice at P12. Yet, in contrast to DKO animals that clearly displayed an oligodendrocyte maturation impairment, the percentage of OPCs and myelinating oligodendrocytes was surprisingly normal in OL CKO mice pointing to an unaffected maturation. However, at all time points OL CKO mice showed a reduced number of Olig2 positive cells indicating an overall decreased oligodendroglia pool size.

Altogether, our studies confirmed a cell-autonomous function of Mct8/Oatp1c1 within the oligodendroglia lineage putatively for early lineage development while the persistent hypomyelination seen in DKO mice is largely a consequence of the overall decreased TH content inside the brain. Ongoing studies are expected to disclose during which developmental time window Mct8 and Oatp1c1 are required to ensure proper oligodendroglia cell lineage commitment and survival thereby ultimately affecting the total number of oligodendrocytes in the murine CNS.