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Scrutinizing the genetic overlap between disorders characterized by disturbed water and ion homeostasis in the brain

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ABSTRACT:

Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC) is a rare infantile-onset leukodystrophy caused by monogenic mutations in *MLC1* or *GLIALCAM.* MLC patients present impaired brain ion and water homeostasis, which can lead to e.g. progressive neurological deterioration. Interestingly, MLC patients with the same mutation can present highly heterogeneous clinical courses, suggesting the existence of additional genetic or environmental factors influencing brain ion and water regulation. To further examine the genetic mechanisms underlying these processes, we analyzed the genetic overlap between the following traits, which are biologically related to ion/water homeostasis: overall brain volume, grey and white matter volume, two white matter microstructure-derived parameters, stroke outcome, and epilepsy risk. SNP-based heritability of these traits ranged from 22.14% and 40.97%, except for stroke outcome, for which the heritability was approximately zero, probably due to small sample size. Genetic correlations between these traits ranged between 0.003 and 0.884. Analysis of local genetic correlations yielded further insight into the shared genetic architecture of these traits. Cross-trait meta-analysis yielded 62 significant genes, among which *VCAN*, which encodes a chondroitin sulfate proteoglycan influencing e.g. water content in several tissues. MAGMA gene-set analysis on the cross-trait meta-analytic results showed significant association with two gene-sets: PI3K/Akt signaling in cancer, and insulin receptor substrate binding. These analyses identified genes that are jointly associated to traits characterized by ion/water imbalance. Whether variation in these genes explains the phenotypic heterogeneity observed in MLC patients, merits further research.

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