Hereditary Parkinsonism and Dystonia with Hypermanganesemia, Polycythemia and Chronic Liver Disease caused by mutations in the *SLC30A10* gene

Vincenzo Bonifati

Department of Clinical Genetics, Erasmus MC Rotterdam, The Netherlands
v.bonifati@erasmusmc.nl

Background

Manganese is essential for several metabolic pathways but becomes toxic in excessive amounts. Manganese levels in the body are therefore tightly regulated, but the responsible proteins remain unknown.

Aim and methods

We studied two consanguineous families with neurologic disorders including juvenile-onset dystonia, adult-onset parkinsonism, severe hypermanganesemia, polycythemia, and chronic hepatic disease, including steatosis and cirrhosis.

Results

We localized the genetic defect by homozygosity mapping and then identified two different homozygous frameshift *SLC30A10* mutations, segregating with disease. *SLC30A10* is highly expressed in the liver and brain, including in the basal ganglia. Its encoded protein belongs to a large family of membrane transporters, mediating the efflux of divalent cations from the cytosol. We show the localization of the SLC30A10 protein in normal human liver and nervous system, and its depletion in liver from one affected individual. Our in silico analyses suggest that SLC30A10 possesses substrate specificity different from its closest (zinc-transporting) homologs. We also show that the expression of SLC30A10 and the levels of the encoded protein are markedly induced by manganese in vitro. The phenotype associated with SLC30A10 mutations is broad, including neurologic, hepatic, and hematologic disturbances. Intrafamilial phenotypic variability is also present. Chelation therapy can normalize the manganesemia, leading to marked clinical improvements.

Conclusions

We show that *SLC30A10* mutations cause a treatable recessive disease with pleomorphic phenotype, and provide compelling evidence that SLC30A10 plays a pivotal role in manganese transport. This work has broad implications for understanding of the manganese biology and pathophysiology in multiple human organs.