

The first inborn error of manganese metabolism caused by mutations in *SLC30A10*, a newly identified manganese transporter

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We have identified an autosomal recessively inherited disorder of manganese metabolism that causes manganese accumulation in liver and brain leading to characteristic MRI brain appearances of hyperintense basal ganglia on T1-weighted sequences. Most affected individuals present in childhood with difficulties walking and fine motor impairment due to dystonia. Movement disorder is accompanied by liver cirrhosis and some patients have died at young age following complications of cirrhosis. Further hallmark features include polycythemia and features of iron depletion such as low ferritin levels and increased total iron binding capacity.

In order to identify the affected gene, we performed homozygosity mapping on two consanguineous families using an Illumina CytoSNP-12 and sequenced the candidate gene on an ABI sequencer. Functional studies in the manganese-sensitive yeast strain $\Delta pmr1$ were performed using Gateway technology (Invitrogen).

Homozygosity mapping identified *SLC30A10* as the affected gene, and homozygous sequence changes were found in all affected individuals. *SLC30A10* had previously been presumed to belong to a class of zinc transporters. However, expression of human wildtype *SLC30A10* in $\Delta pmr1$ rescued growth in high manganese conditions confirming its role in manganese transport. The presence of missense and nonsense mutations in *SLC30A10* failed to restore manganese resistance. Evidently, evolutionary changes in the amino acid sequence of the protein have altered the substrate specificity of the transporter from Zn in yeast to Mn in mammalian cells.

In conclusion, *SLC30A10* is the first recognized human manganese transporter that, when defective, causes a syndrome of hepatic cirrhosis, dystonia, polycythemia and hypermanganesemia.

Biography

Karin Tuschl graduated from the Medical University of Vienna with an MD at the age of 24 years. Following the completion of an MPhil degree at Queen's University Belfast, and the award of a Milupa scholarship at the UCL Institute of Child Health, London she trained as a pediatric academic clinical fellow. She is currently a PhD student at University College London and the Institute of Child Health with the view of completing training in pediatric metabolic medicine in the near future.

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