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COMMENTARY

A Commentary on Identification of novel MLC1 mutations in Chinese patients with megalencephalic leukoencephalopathy with subcortical cysts (MLC)

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Megalencephalic leukoencephalopathy with subcortical cysts (MLC, OMIM 604004) is a rare neurological disorder in children with an autosomal recessive mode of inheritance.[1] Characteristics for the disease are the development of macrocephaly within the first year of life and the delayed onset of slow progressive motor deterioration with ataxia and mild spasticity. In most children this leads to wheelchair dependency in their teens. Mental capacities, however, are relatively spared. Magnetic resonance imaging is diagnostic and typically shows diffuse cerebral white matter signal abnormalities of the affected white matter, and the characteristic subcortical cysts in anterior temporal and frontoparietal areas.[1] In time, the white matter swelling decreases and cerebral atrophy proceeds, whereas the subcortical cysts increase in size and number. Histopathological and electron microscopic examination of a brain biopsy from an MLC patient reveals that the white matter swelling was caused by the presence of countless vacuoles between the outer lamellae of myelin sheaths.[2]

In 2000, Topçu *et al.*[3] showed that the *MLC1* gene is located on chromosome 22qtel. Subsequently, the *MLC1* gene was identified in 2001 by Leegwater *et al.*[4] It should be noted that in about 25% of the patients with typical clinical and magnetic resonance imaging picture, no *MLC1* mutations are found. Several of the families, in which no mutations are found, also do not show linkage with the *MLC1* locus, which suggests at least one other gene to be involved in MLC.[4]

The MLC1 protein is specifically expressed in distal processes of astrocytes called endfeet.[5,6] This specific localization, the number of transmembrane domains, together with a weak insignificant homology between MLC1 and several transporters or channels suggests a possible transporter function of the MLC1 protein. At present functional data are still lacking.

The *MLC1* gene consists of 11 coding exons and a first non-coding exon. It encodes a 377-amino-acids plasma membrane protein with eight transmembrane domains and is highly conserved throughout evolution in vertebrates that produce myelin.[5] Mutations in *MLC1* occur throughout the entire coding region and include all types: splice-site, nonsense, and missense mutations, as well as deletions and insertions. Most families have unique mutations, although a founder effect is present in several communities; that is, the Indian Agarwal community, Askehnazi Jews and patients of Japanese origin.[7–10] Mutation analysis was carried out on Chinese MLC patients for the first time by Wang *et al.*[11] This resulted in 10 mutations including five novel missense mutations, one novel deletion and one novel splice-site mutation. This splice site mutation was found in 3 out of 11 patients and the authors claim a founder effect. To confirm a unique *MLC1* mutation spectrum in Chinese MLC patients, more systemic screening needs to be preformed in a larger patient population as already suggested by the authors. The mutations identified in the study by Wang *et al.*[11] add to the growing list of *MLC1* mutations and are helpful for laboratories performing DNA sequencing for diagnostic purposes.

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